Periodic Behavior in Cardiac Tissue: Dynamics of Spatially Discordant Calcium Alternans

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Periodic Behavior in Cardiac Tissue: Dynamics of Spatially Discordant Calcium Alternans

by

Per Sebastian Skardal

B.A., Boston College, 2008

M.S., University of Colorado Boulder, 2010

A thesis submitted to the

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Periodic Behavior in Cardiac Tissue: Dynamics of Spatially Discordant Calcium Alternans
written by Per Sebastian Skardal
has been approved for the Department of Applied Mathematics

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Date ________________

The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.
The study of cardiac alternans, a phenomenon characterized by beat-to-beat alternations of activity in cardiac tissue that has been directly linked with sudden cardiac arrest, has become an important area of research at the intersection of biology, physics, and mathematics. In this Thesis, we derive and study the spatiotemporal dynamics of a reduced model describing the beat-to-beat evolution of calcium-driven alternans in a periodically-paced cable of tissue. This work can be thought of as an extension of the seminal work of Echebarria and Karma [Physical Review Letters, 88:208101, 2002; Physical Review E, 76:051911, 2007], which was the first analytical treatment of alternans in tissue. While Echebarria and Karma considered the case of alternans driven by a voltage-mediated instability and neglected the effect of calcium dynamics, we extend this approach to the important case of a calcium-mediated instability and account for the effect of bi-directional coupling between voltage and calcium dynamics. Our reduced model consists of two bi-directionally coupled integro-difference equations that describe the amplitude of alternans in calcium and voltage along a cable of tissue. In agreement with detailed ionic models, our reduced model yields three solution regimes separated by two bifurcations. The three regimes are described by (i) no alternans, (ii) smooth wave patterns, and (iii) discontinuous patterns. Due to the smoothing effect of electrotonic coupling on voltage, discontinuous patterns are non-physical in voltage-driven alternans, and thus can only be observed when the instability is mediated by the calcium dynamics. We study spatial properties and dynamics of solutions in each regime, as well as several novel properties of solutions in the third regime. We find that solutions in the third regime are subject to unique memory and hysteresis effects, which are not present in the solutions in the second regime. In addition to symmetrizing the shape of profiles about the phase reversals, or node, we find a novel phenomenon we call *unidirectional pinning*, a mechanism where nodes can be moved towards, but
not away from, the pacing site when parameters are changed. Furthermore, we find that while the spatial wavelength of solutions in the smooth regime scales sub-linearly with the conduction velocity (CV) length scale, the spatial wavelength of solutions in the discontinuous regime scales linearly with this length scale. Due to the tendency for nodes to cause conduction blocks in tissue, we hypothesize that intracellular calcium-driven alternans are more arrhythmogenic than previously believed since they cannot be expelled from the cable due to unidirectional pinning. We complement these analytical results with numerical studies of a detailed, biologically robust ionic model of a cable of cells. We show that our reduced model captures the behavior of these detailed ionic models and can in fact predict their dynamics, and that detailed ionic models display the novel properties found in the reduced model, including unidirectional pinning. This work extends our theoretical understanding of alternans to include the important effect of calcium dynamics. Finally, we make concluding remarks about physiological implications and experiment suggestions as well as discuss possible extensions and future work.
Dedication

To Harald and Eva Skardal, for the unconditional love, support, and belief in me that can only come from parents, and most of all for always encouraging me to keep asking questions.
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There are many people that I have to thank for helping me during my time in Boulder. The first is my fiance Lauren: my muse and support system. For some reason has put up with me all this time. Second, I have a wonderful group of friends/colleagues, most notably my office mates Dane, Dan, and Dan. Our conversations have always been productive, whether they’ve taken place in the office or the pub. Next, I have had wonderful teachers here in Boulder, including my committee members. I’ve also been incredibly lucky to work with plenty of fantastic external collaborators, in particular Ed, Rio, and most of all Alain, who is really the guru for the work presented in this dissertation.

Most importantly, I would like to thank Juan for taking me on and being a great teacher, both in regards to mathematics, as well as being a great person. I’m sure there were plenty of times that I tested your patience (e.g. times I spend working on synchronization when I should have been focusing on cardiac dynamics), but somehow you never showed it. Although you certainly see further than I can, the only reason I have been able to reach this point is because I am standing on the shoulders of a giant.
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Chapter 1

Introduction

Each year, sudden cardiac arrest is responsible for over 300,000 deaths in the United States [28, 61]. This represents roughly half of all heart disease related deaths and is the leading cause of natural death in the United States. Before sudden cardiac arrest occurs, the heart typically transitions from a healthy state known as normal sinus rhythm to arrhythmogenic behavior: first to ventricular tachycardia, then to ventricular fibrillation [28]. During normal sinus rhythm, an electrical wave originating in the sinoatrial node, the heart’s natural pacemaker located at its north pole, propagates through the heart tissue, first through the two atria, then through the two ventricles. This electrical wave causes a synchronized contraction of heart tissue, which in turn allows the heart to pump a sufficient amount of blood throughout the body. In contrast, during ventricular tachycardia the ventricles contract much more rapidly. In ventricular fibrillation contractions occur asynchronously, causing the heart to no longer pump a sufficient amount of blood around the body. Ventricular fibrillation is almost always fatal.

These overwhelming statistics make the study of cardiac arrhythmogenesis an important area of research that lives at the intersection of biology, physics, and mathematics. In the 1980’s, Cohen and collaborators directly linked this kind of arrhythmogenesis and precipitation of sudden cardiac arrest to a phenomenon known as cardiac alternans in a series of laboratory experiments [1, 47, 56]. Cardiac alternans was first observed in 1872 by Traube [58] and is characterized by beat-to-beat alternations of the electronic and chemical behavior of cardiac tissue [29]. Despite the work of Cohen and collaborators, the full mechanism linking cardiac alternans to cardiac arrhythmogenesis and
sudden cardiac arrest has continued to elude researchers. In this Thesis, we will study the dynamical properties of cardiac alternans. As with the majority of other excitable media research [11], the transition from healthy cardiac behavior to arrhythmogenic behavior is spatiotemporal in nature, and therefore we will study the spatiotemporal dynamics of alternans in cardiac tissue. This work can be thought of as an extension of the seminal work of Echebarria and Karma in References [14, 16], where the authors derived and studied a integro-partial differential equation governing the dynamics of alternans dynamics in a cable of heart tissue. Other related work has been published in References [12] and [55], the latter containing some of the material presented in this Thesis.

This Thesis is organized as follows. In the remainder of this chapter, we will describe some basic physiology and cardiology, define cardiac alternans, introduce spatially discordant alternans and describe calcium-driven alternans. In Chapter 2 we will present and describe results from detailed ionic models of cardiac behavior, including both single-cell and spatiotemporal dynamics of alternans. In Chapter 3 we will derive a reduced system of equations describing the beat-to-beat dynamics of alternans in a one-dimensional cable of tissue and describe the resulting dynamics of this system in a numerical survey. In Chapter 4 we will analyze the first regime of solutions, including the onset of alternans and spatial properties. In Chapter 5 we will analyze the second regime of solutions, including spatial properties, and present some of the novel characteristics of these solutions. In Chapter 6 we will revisit the detailed ionic models, showing that our reduced system both qualitatively and quantitatively predicts behavior of ionic model simulations. Finally, in Chapter 7 we will conclude by discussing physiological implications and future work.

1.1 Basic Physiology and Cardiology

Upon a sufficiently strong electrical stimulus, the contraction of a sufficiently rested heart cell occurs through the following chain of events. First, the transmembrane voltage potential $V_m = V_e - V_i$ along the cell membrane depolarizes, where $V_e$ and $V_i$ denote the extra-cellular and intra-cellular voltage potentials. Typical polarized (resting) and depolarized (stimulated) voltage potentials $V_m$ are approximately $-80$ mV and $40$ mV, respectively. The initial electrical stimulus
then triggers activity in several ion channels which initiate a flux of several charged ions across the cell membrane, most importantly sodium $\text{Na}^+$, potassium $\text{K}^+$, and calcium $\text{Ca}^{2+}$. The fluxes of these charged ions entering and exiting the cell themselves contribute to the dynamics of the action potential and will be described in more detail in Chapter 2. Of particular importance to the excitation-contraction process are calcium ions $\text{Ca}^{2+}$, which enters the cell via the L-type calcium current, the primary mechanism for calcium entering the cell, and causes the intracellular calcium concentration $[\text{Ca}^{2+}]_i$ to increase. This in turn causes the sarcoplasmic reticulum (SR), a series of rigid tubule structures inside the cell that store various ions, to release more calcium into the intracellular region in a positive-feedback mechanism. Next, calcium ions inside the intracellular region bind with troponin proteins, which initiates contraction of the cell in a similar fashion to skeletal muscle cells. Following this contraction, the intracellular calcium concentration decreases, the membrane voltage potential re-polarizes, and the cell returns to a resting state until it receives another external stimulus and the cycle repeats [28]. In Figure 1.1 we include a schematic diagram of the structures involved in the process described above. For more details on the excitation-contraction process of cardiac cells, see References [4, 5, 30].

![Figure 1.1: Cellular structures involved in the excitation-contraction process.](image)

Due to their roles in the excitation-contraction process described above, transmembrane voltage and intracellular calcium dynamics are of particular importance to cardiac electrophysiologists.
To quantify the voltage and calcium dynamics at each beat, we will study the action potential duration (APD\textsubscript{n}) and peak calcium concentration (Ca\textsubscript{n}) quantities at each beat \(n\) [29]. APD is defined as the duration of time at each beat a cell remains depolarized, i.e., the time \(V_m\) spends above a chosen threshold value. To be consistent with previous alternans studies, in this Thesis we will choose this critical threshold value to be \(V_c = -40\) mV [16]. Ca is defined as the maximum calcium concentration value attained at each beat. In Figure 1.2 we show typical \(V_m\) and \([Ca^{2+}]_i\) profiles for a healthy cardiac cell paced at a fixed pacing period, or basic cycle length (BCL), of 360 msec. These profiles were obtained from numerical simulations of the Shifox model described in References [54] and [20]. Details of this model will be discussed in Chapter 2. Time series for \(V_m\) and \([Ca^{2+}]_i\) are plotted in blue. We also illustrate the APD and Ca at each beat (subscripts \(n\) and \(n+1\) denote the APD and Ca at the \(n^{th}\) beat, respectively) with red double arrows. Other relevant variables for the voltage dynamics are the diastolic interval (DI\textsubscript{n}), given by the time a cardiac cell spends polarized in between beats \(n\) and \(n+1\), and the activation interval (T\textsubscript{n}), given by the time in between stimuli \(n\) and \(n+1\) [29]. These quantities are illustrated with black double arrows. For the simple case of a single cell paced at a constant BCL, T\textsubscript{n} = BCL for all beats \(n\). Furthermore, it is easy to see from Figure 1.2 that APD\textsubscript{n} + DI\textsubscript{n} = T\textsubscript{n} at each beat. We note that during normal sinus rhythm, assuming a perfectly periodic stimulus and zero noise effects, a cardiac cell displays period-one dynamics, meaning that at steady-state, the characteristics of one beat are identical to those of all other beats. In terms of APD and Ca, this means that APD\textsubscript{n} = APD\textsubscript{n+1} and Ca\textsubscript{n} = Ca\textsubscript{n+1} for all \(n\), such as in Figure 1.2.

1.2 Cardiac Alternans

In sharp contrast to normal cardiac behavior, a cell undergoing cardiac alternans is characterized by alternating behavior in the beat-to-beat behavior of voltage and calcium dynamics [29, 61]. In other words, the voltage and calcium dynamics exhibit long-short-long-short... and large-small-large-small... patterns of activity, respectively. In terms of APD and Ca, this alternating phenomena manifests itself in period-two steady-state dynamics in APD and Ca. In Figure 1.3 we show
Figure 1.2: Typical $V_m$ and $[\text{Ca}^{2+}]_i$ profiles for a simulation of a healthy cardiac cell paced at a BCL of 360 msec. APD and Ca at subsequent beats $n$ and $n+1$ are denoted, along with DI and T.

typical $V_m$ and $[\text{Ca}^{2+}]_i$ profiles for a cardiac cell undergoing alternans paced at a fixed BCL of 340 msec. In Figure 1.3 we plot, respectively, time series for $V_m$ and $[\text{Ca}^{2+}]_i$ dynamics in blue for two subsequent beats and denote the APD and Ca at each beat with red double arrows, noting that both the APD and Ca at beat $n$ are larger than at beat $n+1$. To highlight the alternating behavior of each, we plot the steady-state beat-to-beat alternations of APD and Ca in Figure 1.4.

The example plotted in Figure 1.3 represents the typical case where APD and Ca alternate in phase, i.e., with a long (short) APD at beat $n$ ($n+1$) corresponding to a large (small) Ca at beat $n$ ($n+1$), which is often called “electromechanically concordant alternans” [61]. It should be noted that in some cases APD and Ca can alternate out of phase, i.e., with a long (short) APD at beat $n$ ($n+1$) corresponding to a small (large) Ca at beat $n$ ($n+1$), which is often called “electromechanically discordant alternans” [61]. This typically occurs when the calcium-to-voltage coupling is negative, which will be discussed in more detail in Chapter 2. In this Thesis, however, we will concentrate on the more typical case of locally in phase alternans.

For a single cell, the transition from healthy cardiac behavior to alternans, known as the onset of alternans, is described by a period-doubling bifurcation [29]. Detailed ionic models tend to be very complicated, as will be discussed in Chapter 2, and in turn there are typically many parameters that one can change to achieve a transition to alternans. However, one simple way to
induce alternans is to appropriately decrease the BCL. This can be explained heuristically by the fact that cardiac cells are similar to other muscle cells in that they need a sufficient amount of rest between each contraction. After a full beat, if a cell is not given enough rest, then de-polarization is weak and yields a short action potential. Given the quick re-polarization of this beat, the cell is then allowed more time to rest and is able to depolarize more strongly upon the arrival of the next stimulus, and the pattern repeats. In Figure 1.5 we plot steady-state APD and Ca as a function of BCL, which is decreased from 360 msec to 340 msec in a simulation of the Shifox model, which we describe in greater detail in Chapter 2. A period-doubling bifurcation is evident at the critical BCL value of $BCL^* \approx 350$ msec, which separates period one dynamics for $BCL > BCL^*$ from period-two dynamics for $BCL < BCL^*$.

### 1.3 Spatially Discordant Alternans

Cardiac alternans that occur in isolated cells, as described in the previous section, have received much attention from researchers, but offer little intuition into the origin of cardiac arrhythmias. Rather, we will see that the spatiotemporal dynamics of alternans in patches of tissue are critical in understanding this transition. In particular, recent research has found that in patches
of tissue, alternans can form discordantly [23, 64], i.e., different regions of tissue, both undergoing alternans, alternate with opposite phase. In other words, while tissue in one region alternates in a long-short-long-short... pattern, tissue in another region alternates in a short-long-short-long... pattern. We illustrate the phenomenon of discordant alternans in Figure 1.6 where the red and blue patches of tissue are alternating out-of-phase with short-long... and long-short... patterns, respectively. Discordant regions typically form spontaneously in cardiac tissue exhibiting alternans due to both the underlying dynamics of each cell and the propagation of activity through the tissue [36, 51, 60]. Importantly, there is a thin region of tissue called a nodal line at the border between the two discordant regions observed that exhibits locally period-one behavior. In a broader sense, a nodal line can be thought of as a phase-reversal signaling a transition between out-of-phase states.

In recent years, experimental and numerical research has examined the role of spatially discordant alternans in detail and found that the presence of nodal lines between out-of-phase regions are critical in causing the transition from healthy cardiac behavior to arrhythmogenesis and possible sudden cardiac arrest [49, 61, 62]. Research shows that the presence of nodal lines is dangerous because conduction blocks tend to form nearby, effectively blocking the propagation of activity past portions of a nodal line and creating a structural barrier to normal activity [41]. Once these conduction blocks exist along a portion of the nodal line, activity propagating across other portions of the nodal line tend to re-enter the space behind the conduction blocks, which can give rise to sustained spiral wave activity, ventricular tachycardia, and ventricular fibrillation [44].
In Figure 1.7 we illustrate a commonly accepted mechanism [61] for how the presence of nodal lines in spatially discordant alternans can cause conduction blocks and re-entry. We start by introducing ectopic beats, which are characterized by small groups of nearby cells depolarizing without receiving a stimulus from an oncoming wave of activity. Ectopic beats are typically due to random noise or other fluctuations of internal cell activity and are very common in cardiac tissue, yet they rarely cause any problematic scenarios. However, we will see in what follows that if an ectopic beat occurs in the wrong place at the wrong time in tissue with spatially discordant alternans, in particular near a nodal line, it can potentially trigger a sequence of events that can lead to sudden cardiac arrest. Consider the occurrence of an ectopic beat (denoted as a star) near a nodal line in between two subsequent beats (denoted by the solid arrow). This causes a radial propagation of activity about the position of the ectopic beat. Typically any propagation backwards towards the pacing site is annihilated by oncoming activity. As propagation in the opposite direction crosses the nodal line, it enters tissue at a point in time (denoted by the dashed arrow) where it is not rested enough to depolarize, causing a conduction block of activity. However, when propagation from a more lateral direction crosses the nodal line (denoted by the green arrow) the tissue has had enough time to rest and continues the propagation of activity. In particular, these propagations typically re-enter the now-rested region behind the conduction block, which leads to re-entrant spiral waves,
ventricular tachycardia, ventricular fibrillation, and finally sudden cardiac arrest.

Typically, activity in relatively homogeneous cardiac tissue propagates radially outward from the pacing site. For simplicity, previous analytical treatments of cardiac alternans have studied a one-dimensional cable of tissue of length $L$, where the beginning ($x = 0$) represents the pacing site and the end ($x = L$) represents the end of a patch of tissue [12, 14, 16, 55]. We note that this formulation accurately models the dynamics along long cables of cells called Purkinje fibers, which has been studied experimentally [7, 9]. Thus, a beat begins at $x = 0$ and propagates in the positive $x$ direction until it reaches the end of the cable. Importantly, a phase reversal at a single point on the domain represents the presence of a nodal line. Of particular interest is the formation and behavior of these phase reversals, which we will call nodes.

### 1.4 Calcium-Driven Alternans

Until recently, researchers studying cardiac dynamics assumed that alternans are voltage-driven. In other words, it was assumed that the underlying mechanism driving the period-two dynamics was an instability inherent in the voltage dynamics. This has been in part due to the
fact that laboratory experiments were not precise enough to study the effect of calcium cycling and early ionic models such as those defined in References [3, 38] were limited in that they could not accurately describe the complexity in calcium-cycling dynamics. However, great advances in both experimental techniques and the complexity of ionic models have allowed for more sophisticated studies that show that alternans can indeed be calcium-driven, i.e., mediated by an instability in the calcium-cycling dynamics [6, 10, 37, 42, 46, 54].

Calcium-driven alternans can be observed directly by using a technique known as a voltage-clamp, which corresponds to forcing a fixed, period-one voltage signal. Voltage-clamps can be implemented relatively easily in both laboratory experiments and ionic model simulations. In Reference [10] Chudin et al. implemented a voltage clamp experimentally by measuring the \( V_m \) activity of healthy rabbit cells over a large range of pacing periods. These period-one \( V_m \) signals were then used to pace unhealthy rabbit cells from which calcium alternans were observed.

In terms of ionic models of cardiac activity, the voltage signal to be used in the voltage-clamp can theoretically be obtained by using an Ott, Grebogi, and Yorke control mechanism to maintain and record a period-one voltage signal, even after it has become unstable. However, a much simpler way to implement a voltage clamp in numerical ionic model simulations is to
simulate a cell to steady-state, at which point the cell displays period-two dynamics, and define
the clamped voltage at each beat to be the averaged voltage activity of subsequent beats, i.e.,
\[ V_{\text{clamp}}(t) = \frac{[V_1(t) + V_2(t + BCL)]}{2}, \]
force the voltage at each beat to be \( V_{\text{clamp}}(t) \) and allow the
other variables in the ionic model to evolve freely according to their ODEs.

In figure 1.8 we plot the results from the implementation of the simple numerical voltage-
clamp technique described above using the Shifox model. In Figures 1.8(a) and (b) we plot, re-
spectively, the \( V_m \) and \([\text{Ca}^{2+}]_i\) dynamics at two subsequent beats and denote the APD and Ca at
each beat. We note that while the voltage dynamics are period-one, alternans clearly exist in Ca.
To highlight this, we plot the steady-state beat-to-beat behavior of APD and Ca in Figure 1.9,
noting that APD is truly period one and Ca is truly period-two. These results are in sharp contrast
to the results shown in Figure 1.3 where alternans existed in both APD and Ca and confirm that
alternans can indeed be calcium-driven.

![Figure 1.8: Voltage-clamped dynamics: \( V_m \) and \([\text{Ca}^{2+}]_i\) profiles for a voltage-clamped cardiac cell
undergoing alternans paced at a BCL of 340 msec. APD and Ca at subsequent beats \( n \) and \( n + 1 \)
are denoted, along with their steady-state beat-to-beat oscillations highlighted below. Note that
while voltage is forced to be period-one, calcium alternans still exist.](image)

Calcium-driven alternans have received a great deal of attention from researchers recently
due to their spatial, dynamical, and physiological properties. Spatially, it has been found that
the length-scale of the phase-reversal representing a nodal line is much smaller when alternans
are calcium-driven instead of voltage-driven [52, 63]. Numerically, the length-scale of this phase-
reversal has been found to be as small as spatial discretization allows [52] and analytical methods suggest that these phase-reversals may be infinitely-small, i.e., form a discontinuity in the alternans profiles [55]. These findings have been supported by the discovery of sub-cellular calcium alternans [2, 45], i.e., calcium dynamics alternating discordantly in different regions of the same cell. Furthermore, as we will see later on in this Thesis, other spatial and dynamical properties of nodes can cause calcium-driven alternans to be even more dangerous and arrhythmogenic than voltage-driven alternans.

To date, our theoretical understanding of voltage-driven alternans is well developed [12, 13, 14, 16, 17, 53]. In addition to simply understanding the mechanisms that cause alternans, these analytical studies have also been useful for the sake of guiding the control problem of how we can suppress alternans, and in turn lethal cardiac arrest [9, 15, 21, 25, 27, 32]. On the other hand, our theoretical understanding of calcium-driven alternans remains very limited, as is our understanding of the effects that bi-directional coupling between $V_m$ and $[Ca^{2+}]_i$ dynamics have on alternans in general. Therefore, this Thesis will focus on studying the spatiotemporal dynamics of calcium-driven alternans, where we include bi-directional coupling between the $V_m$ and $[Ca^{2+}]_i$ dynamics. We will primarily treat this problem analytically, but also use ionic model simulations to guide and verify our analytical results.

Figure 1.9: Steady-state APD and Ca for a voltage-clamped cardiac cell undergoing alternans paced at a BCL of 340 msec. Note that while voltage is forced to be period-one, calcium alternans still exist.
Chapter 2

Detailed Models of Cardiac Dynamics

When mathematically modeling cardiac behavior we are primarily concerned with the transmembrane voltage potential $V_m$ as well several intracellular ion concentrations, most notably calcium $[Ca^{2+}]_i$ as well as sodium $[Na^+]_i$ and potassium $[K^+]_i$, due to their importance in the excitation-contraction process described in Chapter 1. Even at the scale of a single cell, the dynamics of these quantities are coupled through nonlinear ODEs, yielding systems of great complexity. First, the voltage potential $V_m$ dynamics is primarily a function of the fluxes of $[Ca^{2+}]_i$, $[Na^+]_i$, and $[K^+]_i$ through the cell membrane. However, activity in the fluxes of $[Ca^{2+}]_i$, $[Na^+]_i$, and $[K^+]_i$ are triggered and react to gating variables that open and close depending on the membrane voltage $V_m$. Finally, there are several currents that contribute to the net flux of each ion concentration $[Ca^{2+}]_i$, $[Na^+]_i$, and $[K^+]_i$ that act on different timescales and contribute to different portions of the heart beat. Thus, accurately and robustly modeling the activity of cardiac cells requires a complicated formulation of many coupled nonlinear processes, and remains a very active area of research [4, 43].

2.1 Detailed Ionic Models for Cardiac Dynamics

The first detailed mathematical model for cardiac activity was the Noble model [38], which is based on the formulation of Hodgkin and Huxley [24] for action potentials in neurons. The Noble model keeps track of sodium and potassium currents and is comprised of four coupled ordinary differential equations. Since this first step, research in the area of modeling cardiac behavior has
progressed, yielding more and more complicated models that more accurately and robustly describe cardiac behavior. A handful of these more complicated models are described in References [3, 18, 20, 33, 34, 35, 54]. Typically, these models are based on a simple formulation for the change in membrane voltage potential

\[
\frac{d}{dt} V_m = -\frac{(I_{ion} + I_{stim})}{C_m},
\]

(2.1)

where \(I_{ion}\) represents the contribution from all ion currents and thus depends on all ion fluxes, \(I_{stim}\) represents any external stimulus given to the cell, e.g. an external periodic pacing, and \(C_m\) is the cell membrane capacitance. In addition to the membrane voltage, it is also important to keep track of intracellular ion concentrations such as calcium \([\text{Ca}^{2+}]_i\), sodium \([\text{Na}^+]_i\), and potassium \([\text{K}^+]_i\). These concentrations often evolve according to their own ODEs, which are coupled to the voltage dynamics in nonlinear ways. Furthermore, in more detailed models the intracellular concentration for one or more ions can be split up into different “compartments” in the cell, in which case several coupled ODEs are needed to describe the ion concentration throughout the entire cell [35, 54]. Furthermore, many ion currents react according to additional gating variables that evolve according to their own ODEs, or are sometimes modeled stochastically.

Models of the type briefly introduced above describe the activity of a single cell in isolation. Thus, when interested in cardiac behavior across an entire patch of tissue, we need to model the activity of many coupled cells and add a spatial component to the system. Typically, this spatial component is added to the voltage dynamics, i.e., Equation (2.1), and not to the ion concentration dynamics, due to the fact that voltage diffuses across tissue, effectively coupling nearby cells, while ion concentrations diffuse on a timescale much slower than a typical heart beat. In particular, we will be interested in modeling a cable of coupled cells, i.e., a one-dimensional domain. Because the size of each cell is small relative to the length of a patch of tissue, we assume a continuous cable of length \(L\) with boundaries at \(x = 0\) and \(x = L\) and modify Equation (2.1) with a diffusive term to obtain the cable equation,

\[
\frac{\partial}{\partial t} V = D_V \frac{\partial^2}{\partial x^2} V - \frac{(I_{ion} + I_{stim})}{C_m},
\]

(2.2)
where $D_V$ is the diffusion coefficient for voltage. The cable is then paced periodically at the end $x = 0$ for a fixed BCL. Furthermore, boundary conditions are typically taken to be no-flux:

$$\frac{\partial}{\partial x} V \bigg|_{x=0} = 0, \quad (2.3)$$

$$\frac{\partial}{\partial x} V \bigg|_{x=L} = 0. \quad (2.4)$$

Thus, models of the type we are interested in consist of a PDE governing the voltage dynamics along an entire cable that effectively couples nonlinear systems of ODEs at each point along the cable. Needless to say, the final result is a system of great complexity, which reflects the cost of biological accuracy and robustness.

For the ionic model simulations used in this Thesis, we have chosen a detailed ionic model known as the Shifox model that combines the ionic currents of Fox et al. [20] and the intracellular calcium cycling of Shiferaw et al. [54]. The data presented in the figures in Chapter 1 were all taken from simulations of this model as implemented in Reference [31]. We have chosen this model because of its robust and detailed description of calcium-cycling dynamics, which in particular produce calcium-driven alternans for a relatively wide parameter range. The Shifox model has also been used in other numerical studies of calcium-driven alternans, such as Reference [31]. Below we will describe a few of the key features and parameter choices of the Shifox model that we have made. For reference, we present the full formulation of the Shifox model in Appendix A.

To ensure that alternans are calcium-driven, we change two parameter values in the original Shifox formulation. First, we set the voltage inactivation timescale parameter $\tau_f = 30 \text{ ms}$. This value is significantly less than the typical value of $\tau_f = 50 \text{ ms}$. This parameter describes the time needed for voltage dynamics to “rest” after re-polarization, and therefore decreasing it impedes voltage-induced initiation of alternans. Second, we set the SR-release slope parameter $u = 9 \text{ ms}^{-1}$, which is larger than the typical value of $u = 5 \text{ ms}^{-1}$. This parameter describes the rate at which calcium is released into the cell by the sarcoplasmic reticulum, and therefore a larger value leads to larger instability in the calcium-cycling dynamics and higher propensity for calcium-alternans. Additionally, we ensure that at each cell the APD and Ca alternans are in phase. To do this, we
make sure the calcium-to-voltage coupling is positive by setting the calcium-induced inactivation exponent $\gamma = 0.2$. Typically $\gamma < 1$ corresponds to positive calcium-to-voltage coupling and $\gamma > 1$ corresponds to negative calcium-to-voltage coupling. Finally, we introduce a scaling constant $\tau$ into the system that scales the timescale for the $j$-gate dynamics in sodium dynamics. Since the influx of sodium is the main contributor for the spiking behavior at the beginning of an action potential, this parameter will not so much affect the dynamics of a single cell, but rather the velocity with which activity propagates through tissue, as we will see shortly. For a more detailed discussion of the specifics of the Shifox model and its parameters, we refer the reader to References [20, 31, 54].

2.2 Amplitude of Alternans and Cable Dynamics

In most alternans research, whether in either a single cell or a cable of tissue, it is often more convenient to study the amplitude of alternans, i.e., the amplitude of oscillations in APD and Ca about their average behavior rather than studying the APD and Ca values themselves. To this end, for observing alternans in ionic model simulations, we introduce the following quantities to measure the amplitude of alternans in APD and Ca:

$$a_n = \frac{APD_n - APD_{n-1}}{APD_n + APD_{n-1}}, \quad (2.5)$$

$$c_n = \frac{Ca_n - Ca_{n-1}}{Ca_n + Ca_{n-1}}. \quad (2.6)$$

These quantities are chosen to correspond to the amplitude we will consider in our reduced model. First, we note that $a_n$ and $c_n$ are non-dimensional quantities. Second, if no alternans exist, i.e., if $APD_{n+1} = APD_n$ and $Ca_{n+1} = Ca_n$, this yields $a_n = 0$ and $c_n = 0$. Finally, these choices naturally symmetrize behavior about zero. In other words, steady-state alternans behavior in a single cell will always be $a_{n+1} = -a_n$ and $c_{n+1} = -c_n$. To illustrate this, we convert the APD and Ca values plotted in Figure 1.5 to $a$ and $c$ and plot the results in Figure 2.1.

To explore how calcium alternans manifest spatiotemporally, we now present computational results from numerically solving the cable equation [Equation (2.2)] with the Shifox model. Along with the parameter values given above, we use a cable of length $L = 15$ cm. Although this is longer
Figure 2.1: Steady-state $a$ and $c$ for BCL decreased from 360 msec to 340 msec. A period-doubling bifurcation corresponding to the onset of alternans is evident at $BCL^* \approx 350$ msec.

than a cable should be in order to accurately model behavior in a real heart, we have chosen a longer cable to illustrate the extended spatial behavior in the dynamics. Here we present steady-state APD and Ca values as a function of a position $x$ along the cable, i.e., functions $APD_n(x)$ and $Ca_n(x)$ where $n$ denotes the beat number and $x$ is the position along the cable. Recall that we assume the cable is paced at a period of BCL ms at the end $x = 0$. We also present the amplitude of APD and Ca alternans along the cable, given by $a_n(x)$ and $c_n(x)$. Finally, we will be interested in the stable steady-state behavior of the profiles $APD(x)$, $Ca(x)$, $a(x)$, and $c(x)$. Since beat-to-beat dynamics evolve slowly in cardiac tissue, each simulation presented below is after a transient of 12000 beats. Below we present one example each from the three regimes of different behavior we have found from numerical surveys.

The first regime consists of steady-state solutions with no alternans along the entire cable. Thus, the stable steady-state dynamics are given by $APD_{n+1}(x) = APD_n(x)$ and $Ca_{n+1}(x) = Ca_n(x)$, or equivalently $a_n(x) = 0$ and $c_n(x) = 0$, for all beats $n$ and all points on the cable $x$. In Figures 2.2 and 2.3 we plot example solutions $APD(x)$, $Ca(x)$, $a(x)$, and $c(x)$ displaying no alternans using $BCL = 370$ ms. We plot subsequent beats $n$ and $n+1$ in red and blue, respectively, noting that the blue dots completely obscure the red dots. Furthermore, the amplitude profiles $a(x)$ and $c(x)$ are identically zero.

Next, as we decrease the BCL we find a transition from the first regime of no alternans
Figure 2.2: Steady-state profiles $APD(x)$ and $Ca(x)$ displaying no alternans for $BCL = 370$ ms.

... to the second regime that displays alternans along the cable. Since this transition marks the beginning of alternans, we refer to it as the onset of alternans. Furthermore, the steady-state profiles $APD(x)$, $Ca(x)$, $a(x)$, and $c(x)$ all form smooth wave patterns. In addition to the beat-to-beat alternation of these profiles, we find that for some sets of parameters these wave patterns travel with a finite velocity towards the pacing site, while for other sets of parameters these wave patterns are stationary. In Figures 2.4 and 2.5 we plot example solutions $APD(x)$, $Ca(x)$, $a(x)$, and $c(x)$ displaying alternans in smooth wave patterns using $BCL = 340$ ms. We plot subsequent beats $n$ and $n + 1$ in red and blue, respectively, to highlight the beat-to-beat alternation. Importantly, each point $x$ along the cable where $a(x) = 0$ and $c(x) = 0$ corresponds to a node, i.e., a phase reversal in the phase of alternans. We note that these smooth wave patterns are analogous to the smooth wave patterns found in cables of tissue where alternans are voltage-driven that were studied in References [14, 16].

Finally, as we decrease the BCL further we find a second transition from the second regime of smooth wave patterns to the third and final regime that displays discontinuous patterns of calcium alternans along the cable, while the voltage alternans remain smooth. This regime of solutions is remarkable for several reasons. First, these solutions are not present in cables of tissue where alternans are voltage driven. Second, regardless of the parameter values, these profiles are
always stationary, i.e., have zero velocity. These solutions manifest themselves in smooth profiles for $APD(x)$ and $a(x)$, but the $Ca(x)$ and $c(x)$ profiles develop large jumps at each node. In our reduced model, we will see that these jumps correspond to actual discontinuities. Furthermore, since profiles are stationary we have that in steady-state $c_{n+1}(x) = -c_n(x)$ and $a_{n+1}(x) = -a_n(x)$. In Figures 2.6 and 2.7 we plot example solutions $APD(x)$, $Ca(x)$, $a(x)$, and $c(x)$ displaying alternans in discontinuous patterns using $BCL = 330$ ms. We plot subsequent beats $n$ and $n + 1$ in red and blue, respectively, to highlight the beat-to-beat alternation. We note the clear discontinuities in the $Ca(x)$ and $c(x)$ profiles.

To summarize, we have numerically found three regimes of qualitatively different solutions of the cable equation. At steady-state, these regimes display (i) no alternans, (ii) smooth wave patterns, and (iii) discontinuous patterns. Regimes (i) and (ii) have been observed in cables where alternans are voltage-driven, while regime (iii) is novel and specific to calcium-driven alternans. We refer to the transition between regimes (i) and (ii) as the onset of alternans, while the transition between regimes (ii) and (iii) corresponds to a novel bifurcation first reported in our paper, Reference [55]. In Chapter 3 we will derive a system of equations that we will use to analytically study these kinds of solutions in Chapters 4 and 5. However, first we introduce two restitution curves that we will use in our derivation.
2.3 Restitution Curves

We now describe two restitution curves that we will use later to derive a reduced system to model the spatiotemporal dynamics of alternans along a cable. The first of these is the APD restitution curve and describes the dependence of the action potential $APD_{n+1}$ on the previous diastolic interval $DI_n$. To illustrate the effect that $DI_n$ typically has on $APD_{n+1}$ we plot in Figure 2.8 the results from changing the DI following a full beat where we can see a clear effect on the next APD. When the DI is relatively large (e.g. blue or red curves), the next APD is also relatively large. However, for a smaller DI (e.g. green and cyan curves), the resulting APD is also significantly smaller. This can be heuristically explained by the fact that after each beat, a heart cell needs a sufficient amount of time to rest. If a cell is not given enough time to rest, then it cannot fire as strongly as normal, resulting in a smaller APD.

The APD restitution relationship can be encapsulated by the function

$$APD_{n+1} = f(DI_n).$$  

(2.7)

In general, this functions depends heavily on the specifics of the ionic model used and is difficult to find analytically. For some simple two-dimensional models of cardiac behavior asymptotic approaches can be used to approximate an analytical form of $f$ as in Reference [16]. However, for
any given model the APD restitution curve can be calculated numerically. This is done using what is known as an S1S2 pacing protocol, which is executed as follows. First, a short cable is paced at \( x = 0 \) for many beats at a large \( BCL = BCL_1 \) until steady-state period-one behavior is realized. Next, the BCL is changed to a smaller value, \( BCL_2 < BCL_1 \) for two full beats. The first APD is just as large as the preceding APDs. However, the following DI and APD are effected by the decrease in BCL and recorded from a location approximately halfway down the cable. This process is repeated for a range of \( BCL_2 \) values, which yields a collection of corresponding (DI,APD) pairs that makes up the APD restitution curve.

We implement this method for computing the APD restitution curve for the Shifox model for typical parameter values and \( \tau = 2 \) msec and plot the results in Figure 2.9. As discussed above, larger DI values yield larger APD values, where the curve is relatively flat. As DI decreases, so does the APD, while the curve become steeper and steeper until it ends, signifying that at such small DI values the cell can no longer depolarize.

The second restitution relationship is the conduction velocity (CV) restitution curve. While the APD restitution curve can in principle be calculated for a single cell, the CV restitution curve requires a spatial component. Assuming that some activity propagates through the tissue at some finite conduction velocity, the CV restitution curve measures the dependence of the CV on DI.
Figure 2.6: Steady-state profiles $APD(x)$ and $Ca(x)$ displaying discontinuous alternans patterns for $BCL = 330$ ms.

This curve is also typically calculated numerically for most models, again using the S1S2 pacing protocol. The only difference in calculating the CV restitution curve is that we track the speed at which a propagation moves through the cable rather than the duration of each action potential. In Figure 2.10 we plot the numerical results using the Shifox model using $\tau = 2$. In fact, the generic shape of the CV restitution is not too dissimilar to that of the APD restitution curve in that larger $DI$ yield larger $CV$ values, and as $DI$ decreases the slope increases. One distinction is that the flat part of the CV restitution curve is much flatter than the flat part of the APD curve.

As we will see in Chapter 3, many parameters of our reduced model will depend on the slopes of both restitution curves, and therefore it will be convenient to have a way to change these slopes. In fact, this is easy to do by simply changing the scaling parameter $\tau$. In Figure 2.11 we show the resulting restitution curves from increasing $\tau$ to 6 and 10. In both restitution curves, the slope along the entire curve becomes steeper as we increase $\tau$. 
Figure 2.7: Steady-state profiles $a(x)$ and $c(x)$ displaying discontinuous alternans patterns for $BCL = 330$ ms.

Figure 2.8: APD restitution: effect of $DI_n$ of $APD_{n+1}$.

Figure 2.9: APD restitution curve for the Shifox model for $\tau = 2$. 
Figure 2.10: CV restitution curve for the Shifox model for $\tau = 2$.

Figure 2.11: Several APD and CV restitution curves for the Shifox model for $\tau = 2, 6,$ and 10.
Chapter 3

A Reduced Model for Calcium-Driven Alternans

The first analytical treatment of cardiac alternans was the pioneering work of Nolasco and Dahlen [39] and Guevara et al. [22], where the onset of alternans in a single cell was explained using the APD restitution curve [Equation (2.7)]. Assuming a constant pacing period $T$, we can use that $DI_n = T - APD_n$ to rewrite Equation (2.7) as

$$APD_{n+1} = f(T - APD_n),$$

so that $APD_{n+1}$ is a function of $APD_n$. For general restitution functions $f$, which are typically taken to be monotonically increasing, the period-one solution $APD_n = APD_{n+1}$ loses stability and gives rise to a period-two solution, i.e., $APD_n = APD_{n+2}$, $APD_n \neq APD_{n+1}$, precisely when the slope of the restitution curve $f'$ exceeds unity, indicating a stable alternating solution of APD, i.e., alternans.

More recent research studying the onset of alternans in a single cell has used other approaches, for instance accounting for memory in the APD restitution function, meaning that $APD_{n+1}$ is not just a function of $DI_n$, but potentially several previous DI and APD values [8, 19, 26]. Mathematically, if $APD_{n+1}$ is a function of potentially the $k + 1$ previous DI and APD values, then this relationship can be captured by the discrete delay equation

$$APD_{n+1} = f(DI_n, \ldots, DI_{n-k}, APD_n, APD_{n-k}).$$

Albeit interesting, the dynamics of a single cell do not suffice to describe the behavior in a cable of tissue. In References [14, 16] Echebarria and Karma used an amplitude equation approach in their analytic treatment of spatiotemporal alternans. Neglecting the effect of calcium dynamics
and assuming a cable of paced tissue of length $L$, they started from the assumption that the $n^{th}$ APD at location $x$ along the cable was governed by

$$APD_n(x) = APD^* + \delta APD + (-1)^n a(x, t), \quad (3.3)$$

where $APD^*$ is the APD at the onset of alternans, $\delta APD$ is a simple shift term that accounts for a deviation in the average APD from $APD^*$, and $a(x, t)$ describes the amplitude of alternans, i.e., the amplitude of deviation from period-one dynamics. Assuming that the amplitude of alternans varies slowly, Echebarria and Karma then proceeded to derive and analyze an integro-partial differential equation that governed the evolution of the amplitude of alternans along the cable, which was also studied in Reference [12]. In what follows we will extend this work by deriving a system of equations that governs the spatiotemporal dynamics of calcium-driven alternans in a cable of tissue.

### 3.1 Derivation of the Equations

Our goal is to derive a system of equations that describes the beat-to-beat dynamics of the amplitude of alternans in APD and Ca along a cable of tissue while (i) assuming that alternans are calcium-driven and (ii) accounting for the bi-directional coupling between the voltage and calcium dynamics. As in References [12, 14, 16], we will assume that the cable is of length $L$ with the pacing site at $x = 0$. Since we are studying the beat-to-beat dynamics on a cable, our system will then be discrete in time but continuous in space. We begin by describing the beat-to-beat evolution of Ca and APD by the general relationships

$$Ca_{n+1}(x) = f_c[Ca_n(x), DI_n(x)], \quad (3.4)$$

$$APD_{n+1}(x) = \int_0^L G(x' - x) f_a[Ca_{n+1}(x'), DI_n(x')] dx'. \quad (3.5)$$

Here $Ca_{n+1}$ depends on a local combination of the Ca and DI at the previous beat, through the function $f_c[Ca_n(x), DI_n(x)]$. On the other hand, $APD_{n+1}$ depends on a non-local combination of the Ca at the current beat and the DI at the previous beat, given by $Ca_{n+1}$ and $DI_n$, respectively, through the smoothed function $f_a[Ca_{n+1}(x'), DI_n(x')]$. We note that APD depends on the present
Ca (rather than the past Ca) due to the fact that the size of an action potential is typically positively correlated with the strength of the $L$-type calcium current and in turn the Ca at the present beat. Furthermore, the function $f_a[Ca_{n+1}(x'), DI_n(x')]$ is smoothed by the Green’s function $G(x' - x)$ to account for the electrotonic coupling that is due to the diffusion of voltage across the cable. In the Appendix of Reference [16] it was shown that this Green’s function exists and was explicitly derived as an “asymmetric Gaussian” given by $G(x' - x) = \tilde{G}(x' - x) + \tilde{G}(x + x') + \tilde{G}(2L - x - x')$, where

$$\tilde{G}(x) = \frac{1}{\sqrt{2\pi\xi^2}}e^{-x^2/2\xi^2} \left[ 1 + \frac{wx}{2\xi^2} \left( 1 - \frac{x^2}{2\xi^2} \right) \right],$$

(3.6)

and the terms $\tilde{G}(x' + x)$ and $\tilde{G}(2L - x - x')$ adjust the Green’s function to account for no-flux boundary conditions. This Green’s function has two intrinsic length scales given by $\xi = \sqrt{D/V_{\text{APD}}}$, which describes the length of electrotonic coupling due to the diffusion of voltage across tissue, and $w = D/V_{\text{CV}}$, which describes the symmetry-breaking effect of the propagation of activity moving in the positive direction. APD* and CV* are APD and CV evaluated at the onset of alternans, and $D_V$ is the diffusion constant of $V_m$ in the standard cable equation (2.2). We note that in general APD* and CV* need to be calculated numerically from one’s ionic model. The role of $G$ in Equation (3.5) is effectively to couple the voltage dynamics nonlocally. We note that no such non-local coupling exists in Equation (3.4) because the diffusion of calcium across tissue is very slow in comparison to a heart beat and can be neglected. Finally, we note that for typical ionic models $w \ll \xi$. Thus, to study the generic behavior of alternans in tissue it typically suffices to study the limit of small $w$.

As in References [14, 16], we seek to study the amplitude of alternans, i.e., not the behavior of APD and CA themselves, but the amplitude of their oscillations about their average behavior. The amplitudes we will consider are given by the non-dimensional quantities

$$c_n = \frac{Ca_n - Ca^*}{Ca^*},$$

(3.7)

$$a_n = \frac{APD_n - APD^*}{APD^*},$$

(3.8)

$$d_n = \frac{DI_n - DI^*}{DI^*}.$$

(3.9)
where \( Ca^*, APD^* \), and \( DI^* \) are \( Ca \), \( APD \), and \( DI \) evaluated at the onset of alternans and \( c_n, a_n, \) and \( d_n \) represent the departures from period-one behavior in \( Ca \), \( APD \), and \( DI \). Note that \( c_n = 0, a_n = 0, \) and \( d_n = 0 \) correspond to no departure from period-one behavior and thus represent the absence of alternans. We note that the amplitudes given in Equations (2.5) and (2.6) were chosen specifically to correspond to Equations (3.7) and (3.8). To see this, we note that in steady-state we have that 
\[
Ca^* \approx \frac{(Ca_{n+1} + Ca_n)}{2} \quad \text{and} \quad APD^* \approx \frac{(APD_{n+1} + APD_n)}{2}.
\]

We now turn to the functions \( f_c \) and \( f_a \), keeping in mind that we wish to describe the generic behavior of alternans in tissue. Therefore, we choose the following phenomenological forms of \( f_c \) and \( f_a \)

\[
f_c(Ca_n, DI_n)/Ca^* = I - rc_n + f(c_n) + \alpha d_n, \tag{3.10}
\]

\[
f_a(Ca_{n+1}, DI_n)/APD^* = 1 + \beta d_n + \gamma c_{n+1}, \tag{3.11}
\]

The forms of \( f_c \) and \( f_a \), grouped into terms I, II, III, and IV, model the following dynamics in the calcium and voltage dynamics. Term I in Equation (3.10) is chosen to model a symmetric period-doubling bifurcation in \( c_n \) and consists of a linear part \(-rc_n\) and a nonlinear part \( f(c_n) \). The parameter \( r \), which multiplies the linear term, governs the stability of \( c_n = 0 \) solutions, and thus is representative of the degree of instability in the calcium dynamics. To connect with the previous work in References [14, 16], we will primarily consider the choice of \( f(c_n) = c_n^3 \). In the absence of term II (i.e., any coupling to the voltage dynamics) this would yield at each point single-cell calcium dynamics governed by

\[
c_{n+1} = -rc_n + c_n^3. \tag{3.12}
\]

Thus, for the single-cell calcium dynamics modeled by Equation (3.12), when \( r < 1 \) the period-one solution \( c_n = 0 \), which represents no alternans, is stable. A period-doubling bifurcation then occurs at \( r = 1 \), followed by symmetric period-two solutions \( c_{n+1} = -c_n \neq 0 \) for \( r > 1 \).

In general the function \( f(c_n) \) in Equation (3.10) need not be a simple cubic, but can contain higher-order terms of odd multiplicity to preserve the symmetry of single-cell dynamics.
−cn. Thus, the more general form of Term I yields single-cell calcium dynamics governed by the polynomial of arbitrary order 2m + 3

\[c_{n+1} = -rc_n + f(c_n)\]  
\[= -rc_n + gc_n^3 + \chi_1c_n^5 + \cdots + \chi_m c_n^{2m+3},\]

where the coefficients \(g, \chi_1, \ldots, \chi_m\) can be chosen to describe the single-cell calcium dynamics of a particular ionic model. We will see that the simple choice \(g = 1, \chi_1, \ldots, \chi_m = 0\) robustly captures the generic dynamics of calcium-driven alternans in a cable, and therefore we will primarily use \(f(c_n) = c_n^3\) in our theoretical analysis. However, as it will prove useful to use other forms of \(f(c_n)\) with higher-order terms, particularly when we use our reduced model to predict behavior of detailed ionic models, we will generalize our theoretical results to the case of more general functions \(f(c_n)\).

Term III captures the dependence of APD alternans on the previous DI, i.e., APD restitution. Since we are assuming that alternans are calcium-driven and not voltage-driven, we assume that \(0 \leq \beta < 1\), so that in the absence of term IV voltage alternans decay to zero. Finally, terms II and IV represent, respectively, the bi-directional coupling of voltage-to-calcium and calcium-to-voltage. While voltage-to-calcium coupling is always positive [61], calcium-to-voltage coupling can be either positive or negative [61]. However, as we discussed in Chapter 1, we will study the typical case of positive calcium-to-voltage coupling where a long (short) APD corresponds to a large (small) Ca at the same beat, so we choose the parameters \(\alpha, \gamma > 0\). Inserting the functions defined in Equations (3.10) and (3.11) into Equations (3.4) and (3.5), we have

\[c_{n+1}(x) = -rc_n(x) + c_n^3(x) + \alpha d_n(x),\]  
\[a_{n+1}(x) = \int_0^L G(x' - x)[\beta d_n(x') + \gamma c_{n+1}(x')]dx'.\]

We now seek to eliminate \(d_n\) from the Equations (3.15) and (3.16), thus closing the dynamics of \(c_n(x)\) and \(a_n(x)\). For this we will use the CV restitution relationship, noting that CV restitution causes the activation interval \(T_n(x)\) to vary along the cable. \(T_n(x)\) is the time in between successive stimuli at a point \(x\) along the cable, and thus is given by the average pacing period BCL at
\( x = 0 \) plus the difference in time it takes for the \( n + 1^{st} \) and \( n^{th} \) stimuli to reach the point \( x \). Mathematically, this relationship is captured by

\[
T_n(x) = BCL + \int_0^x \frac{dx'}{CV[DI_n(x')]} - \int_0^x \frac{dx'}{CV[DI_{n-1}(x')]}.
\tag{3.17}
\]

On the other hand, we have that \( T_n(x) = APD_n(x) + DI_n(x) \). Thus, linearizing Equation (3.17) about the bifurcation point, where \( T^* = BCL \), yields

\[
a_n(x) + d_n(x) = -\frac{CV'(DI^*)}{CV^2(DI^*)} \int_0^x [d_n(x') - d_{n-1}(x')] \, dx'.
\tag{3.18}
\]

Next, as in References [14, 16], we assume that the beat-to-beat dynamics evolve sufficiently slowly, so that \( d_{n-1}(x) \approx -d_n(x) \). We next insert \( d_{n-1}(x) = -d_n(x) \) into Equation (3.18), define \( \Lambda = CV^2(DI^*)/2CV'(DI^*) \), define \( b_n(x) = a_n(x) + d_n(x) \), and differentiate with respect to \( x \), finally obtaining an ordinary differential equation for \( b_n(x) \)

\[
b'_n(x) = -\frac{1}{\Lambda} [b_n(x) - a_n(x)].
\tag{3.19}
\]

Equation (3.19) is linear and can thus be solved analytically using either variation of parameters or an integrating factor. Inserting \( b_n(x) = a_n(x) + d_n(x) \) and noting that at \( x = 0 \) the pacing is periodic, i.e., \( a_n(0) + d_n(0) = 0 \), we finally have that

\[
d_n(x) = -a_n(x) + \frac{1}{\Lambda} \int_0^x e^{(x'-x)/\Lambda} a_n(x') \, dx'.
\tag{3.20}
\]

We now make a few comments about Equation (3.20). First, given the shape of typical CV restitution curves, the parameter \( \Lambda \) tends to be very large, i.e., \( \Lambda \gg 1 \). Second, as we will describe later in this chapter, we will find that steady-state solutions either have no velocity or travel very slowly, in which cases \( d_{n-1}(x) = -d_n(x) \) is either exact or very accurate at steady-state. Thus, the steady-state solutions we will find are valid even far away from the bifurcation point. Finally, in References [14, 16] Echebarria and Karma noted that for voltage-driven alternans the spatial wavelength of solutions scaled as \( \sim \Lambda^{1/2} \) or \( \sim \Lambda^{1/3} \ll \Lambda \), so that Equation (3.20) can be further simplified by using \( e^{(x'-x)/\Lambda} \approx 1 \):

\[
d_n(x) = -a_n(x) + \frac{1}{\Lambda} \int_0^x a_n(x') \, dx'.
\tag{3.21}
\]
However, we will see that calcium-driven alternans admit a new class of solutions not present in
the voltage-driven case where the wavelength of solutions scales like $\sim \Lambda$, and therefore we will use
the full form of Equation (3.20). We finally close the dynamics of $c_n(x)$ and $a_n(x)$ by inserting
Equation (3.20) into Equations (3.15) and (3.16), obtaining

$$
c_{n+1}(x) = -rc_n(x) + c_n^3(x) - \alpha a_n(x) + \frac{\alpha}{\Lambda} \int_0^x e^{(x' - x)/\Lambda} a_n(x') \, dx',
$$

$$
a_{n+1}(x) = \int_0^L G(x' - x) \left[ -\beta a_n(x') + \frac{\beta}{\Lambda} \int_0^{x'} e^{(y - x')/\Lambda} a_n(y) \, dy + \gamma c_{n+1}(x') \right] \, dx'.
$$

(3.22)
(3.23)

In our analysis of the system given by Equations (3.22) and (3.23), we will assume that the
coupling parameters $\alpha$ and $\gamma$, as well as the APD restitution parameter $\beta$, are given. Thus, the
parameters of dynamical importance are the degree of calcium instability $r$ and the CV length scale
$\Lambda$. Furthermore, in addition to the CV length scale $\Lambda$, there are two other length scales given by
the width $\xi$ of the Greens function [Equation (3.6)] and the asymmetry $w$ of the Greens function.
Relative to one another, $\Lambda$ is typically much larger than both $\xi$ and $w$, while $w$ is typically much
smaller than $\xi$, giving a relationship $\Lambda \gg \xi \gg w$. As we noted previously, studying the limit of
small $w$ is typically sufficient for studying generic behavior of alternans, and therefore many of
the figures present in this Thesis will use $w = 0$. Furthermore, in this limit the Green’s function
conveniently becomes a Gaussian distribution with standard deviation $\xi$, which simplifies certain
aspects of our theory as well.

For reference throughout the rest of this Thesis, we summarize the state variables and pa-
rameters, respectively, of our reduced model in Tables 3.1 and 3.2.

<table>
<thead>
<tr>
<th>State Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_n(x)$</td>
<td>amplitude of Ca alternans at beat $n$ at location $x$</td>
</tr>
<tr>
<td>$a_n(x)$</td>
<td>amplitude of APD alternans at beat $n$ at location $x$</td>
</tr>
</tbody>
</table>

Table 3.1: Summary of state variables.

The remainder of this Thesis will focus on analyzing the system given by Equations (3.22)
and (3.23) with regard to the parameters $r$ and $\Lambda$. Next we will present a brief description of the
phase space and describe the nature of solutions of Equations (3.22) and (3.23), and in the following
3.2 Phase Space Description

Before we provide a rigorous analysis of the system given by Equations (3.22) and (3.23), we briefly describe the nature of solutions. Again, we will assume that the parameters $\alpha$, $\beta$, and $\gamma$ as well as the lengthscales $\xi$ and $w$ are given and classify solutions to Equations (3.22) and (3.23) in terms of the parameters $r$ and $\Lambda$. Recall that $r$ represents the degree of instability in the calcium dynamics, with $r = 1$ giving the onset of alternans in a single cell [see Equation (3.12)], and $\Lambda$ is inversely proportional to the slope of the CV restitution curve.

At small values of $r$, we find that the only stable solution of Equations (3.22) and (3.23) is $c(x) \equiv 0$, $a(x) \equiv 0$. Recall that $c(x)$ and $a(x)$ represent the departure from period-one dynamics in the calcium and voltage dynamics at point $x$ along the cable, so these zero solutions correspond to healthy cardiac behavior with no alternans throughout the entire cable. In Figure 3.1 we show an example solution $c(x) \equiv 0$ and $a(x) \equiv 0$ at steady-state obtained using the parameters $r = 0.7$, $\Lambda = 15$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$ on a cable of length $L = 20$.

Next, as $r$ is increased, we find a first bifurcation at which point identically zero solutions lose stability and steady-state $c(x)$ and $a(x)$ form smooth wave patterns that alternate (i.e., flip sign) at each beat. We denote this bifurcation by the critical value $r = r_1(\Lambda)$, where we make explicit that this critical bifurcation value is a function of $\Lambda$. These smooth wave patterns oscillate between positive and negative values throughout the cable, and we note that the points where $c(x)$

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r$</td>
<td>degree of calcium instability</td>
</tr>
<tr>
<td>$\Lambda$</td>
<td>lengthscale of CV restitution</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>voltage→calcium coupling</td>
</tr>
<tr>
<td>$\beta$</td>
<td>slope of APD restitution</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>calcium→voltage coupling</td>
</tr>
<tr>
<td>$\xi$</td>
<td>lengthscale of electrotonic coupling</td>
</tr>
<tr>
<td>$w$</td>
<td>lengthscale of asymmetry in electrotonic coupling</td>
</tr>
</tbody>
</table>

Table 3.2: Summary of system parameters.
Figure 3.1: A no alternans solution $c(x) \equiv 0$ and $a(x) \equiv 0$ of Equations (3.22) and (3.23) for small $r$ values. Parameters are $r = 0.7$, $\Lambda = 15$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.

and $a(x)$ pass though zero correspond to locally period-one behavior, i.e., the presence of nodes. Furthermore, these smooth wave patterns can be either stationary or travel with some finite velocity towards the pacing site. Typically, when the asymmetry $w$ in the Green’s function is small, the wave patterns travel, and if $w$ is large enough they are stationary. See Reference [16] for an analysis of the analogous result in the voltage-driven case. In Figure 3.2 we show an example solution of smooth traveling wave patterns of $c(x)$ and $a(x)$ at steady-state obtained using the parameters $r = 0.85$, $\Lambda = 15$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$ on a cable of length $L = 20$.

Finally, when $r$ is increased further, we find a second bifurcation at which the smooth wave patterns lose stability and $c(x)$ develops a jump discontinuity at each node. We denote this bifurcation by the critical value $r = r_2(\Lambda)$, where we again make explicit that this critical bifurcation value is a function of $\Lambda$. These discontinuous patterns display a wide range of rich dynamics which will be explored in Chapter 5. While steady-state $c(x)$ patterns are no longer continuous, $a(x)$ remains smooth due to the smoothing effect of the Green’s function. Regardless of whether the smooth wave patterns preceding the bifurcation at $r_2(\Lambda)$ were stationary or traveling, the discontinuous solutions are always stationary. As we will see in Chapter 5, the characteristics of solutions in the discontinuous regime vary greatly from those in the smooth regime. In Figure 3.3 we show an example steady-state solution from the discontinuous regime obtained using the parameters $r = 1.15$,
Figure 3.2: A smooth alternans solution $c(x)$ and $a(x)$ of Equations (3.22) and (3.23) for intermediate $r$ values. Parameters are $r = 0.85, \Lambda = 15, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \text{and } w = 0$. Arrows denote movement towards the pacing site at $x = 0$.

\[ c(x) \]

\[ a(x) \]

\[ \Lambda = 15, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \text{and } w = 0 \text{ on a cable of length } L = 20. \]

To provide a clear description of the nature of solutions depending on the parameters $r$ and $\Lambda$, we perform a thorough numerical survey of Equations (3.22) and (3.23) as we vary $r$ and $\Lambda$. Using parameter values $\alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \text{and } w = 0$, we plot the results in Figure 3.4. We label regions of parameter space with zero, smooth, and discontinuous solutions (colored blue, yellow, and red, respectively) and denote the bifurcations describing the transitions from zero to smooth solutions, $r_1(\Lambda)$, and from smooth to discontinuous solutions, $r_2(\Lambda)$.

The next two chapters will focus on a mathematical analysis of the solutions of Equations (3.22) and (3.23). In Chapter 4 we study the onset of alternans, given by the bifurcation at $r_1(\Lambda)$, as well as spatial characteristics of the smooth wave patterns. In Chapter 5 we will study the transition from smooth wave patterns to discontinuous patterns, given by the bifurcation at $r_2(\Lambda)$, as well as several remarkable characteristics of the discontinuous patterns.
Figure 3.3: A discontinuous alternans solution $c(x)$ and $a(x)$ of Equations (3.22) and (3.23) for large $r$ values. Parameters are $r = 1.15$, $\Lambda = 15$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.

Figure 3.4: A description of the nature of steady-state solutions to Equations (3.22) and (3.23) as a function of $r$ and $\Lambda$, obtained from a thorough numerical survey. As $r$ increases, solutions transition from identically zero, to smooth wave patterns, to discontinuous patterns. Other parameters are $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$. 
Chapter 4

Analysis of Smooth Alternans Profiles

In the previous chapter we derived a reduced system of coupled integro-difference equations, given by Equations (3.22) and (3.23), that models the spatiotemporal dynamics of calcium-driven alternans in a cable of tissue. This system of coupled equations is much simpler than the high-dimensional systems of ODEs discussed in Chapter 2 that are coupled through the cable equation [i.e., Equation (2.2)] and is treatable by analytical methods. In this chapter we begin a mathematical analysis of Equations (3.22) and (3.23).

Recall that as we increase the degree of instability in the calcium dynamics, the three solution regimes are the no-alternans regime, where the stable steady-state solutions for the alternans amplitudes $c_n(x)$ and $a_n(x)$ are identically zero, the smooth regime, where $c_n(x)$ and $a_n(x)$ form smooth wave profiles along the tissue, and the discontinuous regime, where $c_n(x)$ develops jump discontinuities at each node. In this chapter we will analyze the onset of alternans, characterized by the transition from the no-alternans regime to the smooth regime, and the dynamics of solutions in the smooth regime. In the first section of this chapter we will use a perturbative approach to studying this bifurcation when the APD restitution parameter $\beta$ is zero. In the second section we will study the spatial properties of solutions in the smooth regime, notably the velocity and wavelength. In the third section we will generalize to the case of a non-zero APD restitution parameter $\beta$. Although we are interested in the generic spatiotemporal dynamics of calcium-driven alternans and will focus on the case of zero asymmetry $w$ in the Greens function, the theory described below can be extended to the case where $w \neq 0$. For reference, we briefly present a sketch of these results.
4.1 Onset of Alternans

The onset of alternans is characterized by the transition from stable to unstable solutions of the form $c_n(x) \equiv 0$ and $a_n(x) \equiv 0$. Therefore, to calculate this transition we seek the curve in $(r, \Lambda)$ parameter space where the solution $c_n(x) \equiv 0$ and $a_n(x) \equiv 0$ loses stability. Thus, we will perform a linear stability analysis about the zero solution. For simplicity we will first assume that the APD restitution parameter $\beta$ is zero. Furthermore, our linear stability analysis is valid for the limit of long cables, i.e., large $L$. However, results from simulations plotted below are from cables of shorter, more realistic lengths and match up very well with our theory.

To begin the linear stability analysis about the zero solution, we will study the evolution of small perturbations of the form $\delta c_n(x) = c\lambda^n e^{ikx}$ and $\delta a_n(x) = a\lambda^n e^{ikx}$ for $c, a \ll 1$, i.e., perturbations with a (possibly complex) growth parameter $\lambda$ whose logarithm $\log \lambda$ gives the growth parameter and a (possibly complex) wave number $k$. Since we seek the transition from stable zero solutions to unstable zero solutions, we will look for a growth parameter of unit magnitude, i.e., $|\lambda| = 1$. Additionally, since the CV parameter $\Lambda$ is typically very large, we define $\epsilon = 1/\Lambda$ such that $\epsilon \ll 1$ is a small parameter. Inserting these forms of $c_n(x)$ and $a_n(x)$ into Equation (3.22) yields, to first order in $a$ and $c$,

$$(ik + \epsilon)c(\lambda + r) = -\alphaika.$$  

(4.1)

We next insert these forms into Equation (3.23) and take advantage of the fact that the Green’s function is Gaussian with standard deviation $\xi$, obtaining

$$a = \gamma ce^{-k^2\xi^2/2}.$$  

(4.2)

Combining Equations (4.1) and (4.2) we eliminate the constants $c$ and $a$ and rearrange to solve for the growth parameter $\lambda$ as a function of the wave number $k$:

$$\lambda = -r - \eta \frac{ik}{ik + \epsilon} e^{-k^2\xi^2/2},$$  

(4.3)
where $\eta = \alpha \gamma$. Equation (4.3) can be interpreted as the dispersion relation describing the growth parameter $\lambda$ for a perturbation of a particular wave number $k$.

We now recall that our domain is a finite cable. Thus, if an instability has some finite group velocity, i.e., grows inside of a traveling envelope, then any growing perturbation will disappear through the boundaries of the cable in finite time. This is known as a convective instability and is characterized by the condition $\partial \lambda/\partial k \neq 0$. Rather, we are interested in instabilities with zero group velocity so that any perturbation will grow inside of a stationary envelope, and thus will remain within the domain. This is known as an absolute instability and is characterized by the condition $\partial \lambda/\partial k = 0$ [16, 50].

Enforcing the constraint $\partial \lambda/\partial k = 0$ on Equation (4.3) yields an additional equation

$$\epsilon = k^2 \xi^2 (ik + \epsilon).$$

(4.4)

Equation (4.4) can be interpreted as the relationship between the wave number $k$ that loses stability first and the small parameter $\epsilon$. We proceed by solving Equation (4.4) perturbatively. In doing so, it is convenient to introduce the new variables $z = k \xi$ and $u^3 = \epsilon \xi$, which transforms Equation (4.4) to

$$u^3 = z^2 (iz + u^3),$$

(4.5)

which has solutions

$$z = i^{-1/3} u - \frac{1}{3i} u^3 + \mathcal{O}(u^5).$$

(4.6)

Returning to the growth parameter in Equation (4.3), we find that

$$\lambda = -r - \eta \left( \frac{iz}{iz + u^3} \right) e^{-z^2/2},$$

(4.7)

$$= -r - \eta \left[ 1 - \frac{3i}{2} u^2 + \frac{13i}{4} u^3 + \mathcal{O}(u^4) \right],$$

(4.8)

$$= -r - \eta \left\{ 1 - \frac{3i}{2} \left( \frac{\xi}{\Lambda} \right)^{2/3} + \frac{13i}{8} \left( \frac{\xi}{\Lambda} \right)^{4/3} + \mathcal{O} \left[ \left( \frac{\xi}{\Lambda} \right)^{2} \right] \right\},$$

(4.9)
where $\xi/\Lambda$ is a non-dimensional quantity that describes the ratio of the length scale of electrotonic coupling to the length scale of CV restitution. Finally, to find the onset of alternans we set the magnitude of the growth parameter to one, $|\lambda| = 1$. This yields that the onset of alternans occurs at

$$r = r_1(\Lambda) = 1 - \eta + \eta^2 \left( \frac{\xi}{\Lambda} \right)^{2/3} + O \left[ \left( \frac{\xi}{\Lambda} \right)^{4/3} \right].$$

(4.10)

To verify these results we simulate Equations (3.22) and (3.23) numerically for several parameter values to find the onset of alternans and compare with our theoretical result, given by Equation (4.10). To find the onset of alternans in simulations for a fixed value of $\Lambda$, we start at a small value of $r$ (i.e., in the no alternans regime) and perturb $c_n(x)$ and $a_n(x)$ as we slowly increase $r$ until perturbations no longer decay. We repeat this for values of $\Lambda$ ranging from 5 to 30. In Figure 4.1 we plot the results from these simulations (connected blue circles) versus our theoretical prediction (dashed red curve), noting that the results agree extremely well. We label the regions $r < r_1(\Lambda)$ and $r > r_1(\Lambda)$ “no alternans” and “alternans”, respectively, to emphasize that the no alternans solution is stable and unstable in the respective regions. Other parameter values are $\alpha, \gamma = \sqrt{0.3}$ ($\eta = 0.3$), $\beta = 0$, $\xi = 1$, and $w = 0$.

![Figure 4.1: The critical bifurcation value $r_1(\Lambda)$ describing the onset of alternans in a cable of tissue mediating a transition between no alternans and smooth wave patterns in the amplitude of alternans as computed from numerical simulation of Equation (3.22) and (3.23) (connected blue circles) vs the theoretical prediction of Equation (4.10). Parameters used are $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.](image-url)
Before proceeding to study the spatial properties of solutions in the smooth regime, we briefly discuss how these results translate to the case of more general nonlinearities in the single-cell calcium dynamics. Recall that this generalization is equivalent to replacing \( c^3_n(x) \) in Equation (3.22) with \( f[c_n(x)] \), where

\[
f(c) = g c^3 + \chi_1 c^5 + \cdots + \chi_m c^{2m+3}.
\]  

(4.11)

Given the perturbations \( c_n(x) \) and \( a_n(x) \) of order \( c, a \ll 1 \) that we used to obtain Equation (4.1) and (4.2), we find that the contribution from the general form of \( f(c) \) remains \( O(c^3) \). Thus, in our linear analysis near onset of alternans we again neglect the effect of these nonlinear terms and recover Equation (4.1). The remainder of the analysis for the onset of alternans then remains unchanged, yielding the same onset of alternans \( r_1(\Lambda) \), as well as growth parameter \( \lambda \) and wave number \( k \). Furthermore, in the analysis that follows we will describe the spatial wavelength \( \lambda_s \) and velocity \( v \) of solutions. As we will see, these quantities depend on the growth parameter \( \lambda \) and wave number \( k \), and therefore these results remain unchanged for more general forms of nonlinearity \( f(c) \) as well.

### 4.2 Spatial Properties

We now study the spatial properties of steady-state solutions in the smooth regime, in particular the spatial wavelength and velocity of profiles. As in the previous section we will first assume that the APD restitution parameter \( \beta \) is zero. We first present a thorough numerical survey of the spatial wavelength and velocity of solutions near the onset of alternans. In Figure 4.2 we plot the wavelength and velocity as computed directly from numerical simulations of Equations (3.22) and (3.23) over a range of \( r \) and \( \Lambda \). Other parameters are \( \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \) and \( w = 0 \). Values are color-coded by the color bars, and black regions correspond to no alternans solutions. The bifurcation corresponding to the border between no alternans and smooth wave patterns, as studied in the previous section, is well described by Equation (4.10). We note that as \( \Lambda \) is increased along the bifurcation curve, the spatial wavelength \( \lambda_s \) and velocity \( v \) increase and decrease, respectively.
We consider solutions very near onset so that steady-state solutions are well-described by $c_n(x) \propto \lambda^n e^{ikx}$ and $a_n(x) \propto \lambda^n e^{ikx}$, where the growth factor $\lambda$ has approximately unit magnitude and $k$ is the wavenumber given by [from Equation (4.6) recalling that $z = k\xi$ and $u^3 = \xi/\Lambda$],

$$\xi k = i^{-1/3} \left( \frac{\xi}{\Lambda} \right)^{1/3} \left[ 1 - \frac{1}{3i} \left( \frac{\xi}{\Lambda} \right)^{1/3} \right] + O \left[ \left( \frac{\xi}{\Lambda} \right)^{5/3} \right]. \quad (4.12)$$

Separating the wave number into real and imaginary parts, $k = k_{Re} + ik_{Im}$, we have that $c_n(x) \propto e^{-k_{Im}x} e^{ik_{Re}x}$, giving a spatial wavelength of $\lambda_s = 2\pi/k_{Re}$. Combining this and Equation (4.12), we have that to leading order the spatial wavelength is

$$\lambda_s = \xi \frac{4\pi}{\sqrt{3}} \left( \frac{\Lambda}{\xi} \right)^{1/3}. \quad (4.13)$$

To find the velocity of the wave patterns, we use that the growth parameter $\lambda$ has unit magnitude, so that if $\lambda = -e^{i\Omega}$ then $c_n(x) \propto e^{-k_{Im}x} e^{ik_{Re}(x+n\Omega/k_{Re})}$. Thus, the velocity (in the negative direction, i.e., towards the pacing site) is given by $v = \Omega/k_{Re}$. To estimate $\Omega$, we note that $-\lambda = \cos \Omega + i \sin \Omega$. Using the form of the growth parameter from the previous section, this
yields

$$\Omega \approx -\lambda_{Im} = \frac{\sqrt{3}}{2} \eta \left\{ \frac{3}{2} \left( \frac{\xi}{\Lambda} \right)^{2/3} + \frac{13}{8} \left( \frac{\xi}{\Lambda} \right)^{4/3} + \mathcal{O}\left[ \left( \frac{\xi}{\Lambda} \right)^2 \right] \right\}. \quad (4.14)$$

To leading order the velocity is given by

$$v = \frac{3\eta \xi}{2} \left( \frac{\xi}{\Lambda} \right)^{1/3} - \frac{13\eta \xi}{8} \left( \frac{\xi}{\Lambda} \right). \quad (4.15)$$

To verify these results we simulate Equations (3.22) and (3.23) numerically for several parameter values to find the spatial wavelength and velocity of solutions at the onset of alternans and compare with our theoretical results given by Equations (4.13) and (4.15). In Figure 4.3 we plot the results from these simulations (connected blue circles) vs our theoretical prediction (dashed red), noting that the results match up extremely well. Other parameter values are \(\alpha, \gamma = \sqrt{0.3}\) (\(\eta = 0.3\)), \(\beta = 0\), \(\xi = 1\), \(w = 0\), and \(L = 40\).

4.3 Non-Zero APD Restitution

We now generalize these results to a non-zero APD restitution parameter \(\beta\). We note that this greatly complicates the equations presented below, although the general scaling results found
in the previous section are recovered. Again, we begin by assuming perturbations of the form 
\[ c_n(x) = c\lambda^n e^{ikx} \] and \[ a_n(x) = a\lambda^n e^{ikx} \]. The result from inserting these into Equation (3.22) yields

Equation (4.1), while inserting these into Equation (3.23) now yields for \( \beta \neq 0 \)
\[
\gamma \lambda e^{-k^2\xi^2/2} = \left[ \lambda + \left( \beta - \frac{\beta\epsilon}{ik + \epsilon} \right) e^{-k^2\xi^2/2} \right] a. \tag{4.16}
\]

By combining Equations (4.1) and (4.16), we eliminate \( c \) and \( a \) and obtain the following quadratic equation for \( \lambda \):
\[
(ik + \epsilon) \left[ \lambda e^{k^2\xi^2/2} + \beta - \frac{\beta\epsilon}{ik + \epsilon} \right] (\lambda + r) = -i\epsilon\lambda. \tag{4.17}
\]

Choosing the root of Equation (4.17) which recovers Equation (4.3) in the limit \( \beta \to 0 \) yields
\[
2\lambda = -r - \frac{ik(\beta + \eta)}{ik + \epsilon} e^{-k^2\xi^2/2} - \frac{\sqrt{r^2(ik + \epsilon)^2 - 2i\epsilon e^{-k^2\xi^2/2}kr(ik + \epsilon)(\beta - \eta) - e^{-k^2\xi^2/2}(\beta + \eta)^2}}{ik + \epsilon}. \tag{4.18}
\]

Surprisingly, the condition \( \frac{\partial \lambda}{\partial \epsilon} = 0 \) for an absolute instability yields the same constraint given by Equation (4.4), which in terms of the variables \( z = \xi k \) and \( u^3 = \xi \epsilon \) has a solution given by

Equation (4.6). Inserting Equation (4.6) into Equation (4.18) yields
\[
\lambda = \frac{-r - \eta - \beta - \sqrt{(r - \beta)^2 + 2(r + \beta)\eta + \eta^2}}{2} + \frac{3}{2} m^{-2/3} \left[ \eta + \beta + \frac{r(\eta - \beta) + (\eta + \beta)^2}{\sqrt{r^2 + 2r(\eta - \beta) + (\eta + \beta)^2}} \right] u^2
\]
\[
- \frac{13}{16} m^{-4/3} \left[ \eta + \beta + \frac{r^3(\eta - \beta) + 3r(\eta - \beta)(\eta + \beta)^2 + (\eta + \beta)^4}{(r^2 + 2r(\eta - \beta) + (\eta + \beta)^2)^{3/2}} \right] u^4
\]
\[
+ \mathcal{O}(u^6) \tag{4.19}
\]
\[
= \frac{-r - \eta - \beta - \sqrt{(r - \beta)^2 + 2(r + \beta)\eta + \eta^2}}{2} + \frac{3}{4} m^{-2/3} \left[ \eta + \beta + \frac{r(\eta - \beta) + (\eta + \beta)^2}{\sqrt{r^2 + 2r(\eta - \beta) + (\eta + \beta)^2}} \right] \left( \frac{\xi}{\Lambda} \right)^{2/3}
\]
\[
- \frac{13}{16} m^{-4/3} \left[ \eta + \beta + \frac{r^3(\eta - \beta) + 3r(\eta - \beta)(\eta + \beta)^2 + (\eta + \beta)^4}{(r^2 + 2r(\eta - \beta) + (\eta + \beta)^2)^{3/2}} \right] \left( \frac{\xi}{\Lambda} \right)^{4/3}
\]
\[
+ \mathcal{O} \left[ \left( \frac{\xi}{\Lambda} \right)^2 \right]. \tag{4.20}
\]
By setting the complex magnitude of the growth parameter $\lambda$ to one, we find that the critical value $r_1(\Lambda)$ is given implicitly by

$$1 = \frac{1}{4} \left( r + \eta + \beta + \sqrt{(r - \beta)^2 + 2(r + \beta)\eta + \eta^2} \right)^2$$
$$+ \frac{3}{8} \left( -r - \eta - \beta - \sqrt{(r - \beta)^2 + 2(r + \beta)\eta + \eta^2} \right)$$
$$\times \left( \eta + \beta + \frac{r(\eta - \beta) + (\eta + \beta)^2}{\sqrt{r^2 + 2r(\eta - \beta) + (\eta + \beta)^2}} \right) \left( \frac{\xi}{\Lambda} \right)^{2/3}.$$ (4.21)

Equation (4.21) defines $r$ implicitly and can be solved numerically. We also note that in the limit $\beta \to 0$, Equation (4.21) can be rearranged to recover Equation (4.10).

To verify this, we compare results from numerical simulation of Equations (3.22) and (3.23), finding the onset of alternans as we did previously, to the theoretical results obtained from solving Equation (4.21) numerically using a bisection method for many $\Lambda$ values. In Figure 4.4 we plot the results from these simulations (connected blue circles) versus our theoretical prediction (dashed red curve), noting that the results agree extremely well. Other parameter values are $\alpha, \gamma = \sqrt{0.3}$ ($\eta = 0.3$), $\beta = 0.2$, $\xi = 1$, and $w = 0$. We again label the regions $r < r_1(\Lambda)$ and $r > r_1(\Lambda)$ “no alternans” and “alternans”, respectively, to emphasize that the no alternans solution is stable and unstable in the respective regions. We find that a non-zero APD restitution parameter $\beta$ effectively decreases the critical value $r_1(\Lambda)$, meaning that the onset of alternans happens earlier.

To find the spatial properties of smooth wave patterns, we use the same approach as in the previous section. Using that $c_n(x) \propto \lambda^n e^{ikx}$, we still have that the spatial wavelength is given by $\lambda_s = 2\pi/k_{Re}$ and the velocity is given by $v = \Omega/k_{Re}$, where $\Omega \approx \lambda_{Im}$. We note that for non-zero $\beta$ the absolute instability condition $\frac{\partial \lambda}{\partial k} = 0$ yielded the same constraint [i.e., Equation (4.4)], which in turn yield the same wave number $k$. Thus, the wavelength given by Equation (4.13) holds for non-zero APD restitution $\beta$. Next, using the growth parameter from Equation (4.20), we have that
Figure 4.4: The critical bifurcation value $r_1(\Lambda)$ describing the onset of alternans in a cable of tissue mediating a transition between no alternans and smooth wave patterns in the amplitude of alternans as computed from numerical simulation of Equation (3.22) and (3.23) (connected blue circles) vs the theoretical prediction of Equation (4.10) for a nonzero APD restitution parameter $\beta$. Parameters used are $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0.2$, $\xi = 1$, and $w = 0$.

for non-zero APD restitution parameter $\beta$, the velocity is given by

$$v = \frac{3\xi}{4} \left( \eta + \beta + \frac{r(\eta - \beta) + (\eta + \beta)^2}{\sqrt{r^2 + 2r(\eta - \beta) + (\eta + \beta)^2}} \right) \left( \frac{\xi}{\Lambda} \right)^{1/3}$$

$$- \frac{13\xi}{16} \left( \eta + \beta + \frac{r^3(\eta - \beta) + 3r(\eta - \beta)(\eta + \beta)^2 + (\eta + \beta)^4 + r^2 \left( 3\eta^2 + \frac{10}{13}\eta\beta + 3\beta^2 \right) }{r^3 + 2r(\eta - \beta) + (\eta + \beta)^2} \right)^{3/2} \left( \frac{\xi}{\Lambda} \right)$$

$$+ O \left[ \left( \frac{\xi}{\Lambda} \right)^{5/3} \right].$$

(4.22)

We note that for small $\beta$, the first term in Equation (4.22) can be expanded as

$$v = \frac{3\xi}{2} \left[ \eta + \left( 1 - \frac{r^2}{(r + \eta)^2} \right) \beta \right] \left( \frac{\xi}{\Lambda} \right)^{1/3} + O \left[ \beta \left( \frac{\xi}{\Lambda} \right)^{1/3}, \left( \frac{\xi}{\Lambda} \right) \right].$$

(4.23)

Thus, when $\beta$ is increased from zero the velocity at onset of alternans also increases.

To verify these results we simulate Equations (3.22) and (3.23) numerically for several parameter values to find the spatial wavelength and velocity of solutions at the onset of alternans and compare with our theoretical results given by Equations (4.13) and (4.22). In Figure 4.5 we plot the results from these simulations (connected blue circles) vs our theoretical prediction (dashed red). For the most part, results agree extremely well, however we note that the approximation of the velocity $v$ for small $\Lambda$ values is not as accurate as for the $\beta = 0$ case. Other parameter values
are $\alpha, \gamma = \sqrt{0.3}$ ($\eta = 0.3$), $\beta = 0.2$, $\xi = 1$, and $w = 0$. We confirm that non-zero APD restitution has no effect on the spatial wavelength $\lambda_s$ of solutions, but causes wave patterns to move with a faster velocity $v$.

Figure 4.5: Spatial wavelength and velocity of solutions at the onset of alternans in a cable of tissue as computed from numerical simulation of Equation (3.22) and (3.23) (connected blue circles) vs the theoretical prediction of Equations (4.13) and (4.22) for a non-zero APD restitution parameter $\beta$. Parameters used are $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0.2$, $\xi = 1$, and $w = 0$.

4.4 Connection to Voltage-Driven Alternans

Now that we have studied the onset of alternans in a cable of tissue as well as the spatial properties of the smooth wave patterns that arise after this bifurcation, we compare and contrast the dynamics of calcium-driven alternans and voltage-driven alternans. When alternans are voltage-driven, the amplitude of alternans forms smooth wave profiles along the cable [16], very similar to the wave patterns we find in the smooth regime of calcium-driven alternans.

First, because the system studied by Echebarria and Karma in Reference [16] was continuous in time, their degree of instability $\sigma$ corresponds to $r - 1$ in our reduced model. Converting parameters appropriately, the onset of voltage-driven alternans in their case is then given by $r_1(\Lambda) = 1 + \frac{3}{4} \left( \frac{\xi}{\Lambda} \right)^{2/3}$. We note that this is equivalent to our result given in Equation (4.10) up to a shift and scaling of $\eta$, a parameter that did not exist in Reference [16]. Thus, we conclude that positive-positive bi-directional coupling between voltage and calcium dynamics promote alternans in tissue.
Furthermore, the spatial wavelength $\lambda_s$ and velocity $v$ at onset for voltage-driven alternans turns out to be the same as for calcium-driven alternans, i.e., Equations (4.13) and (4.15). Thus, we conclude that calcium-driven alternans in the smooth region are analogous in many ways to those of voltage-driven alternans.

We also note that when we account for a non-zero asymmetry parameter $w$ in the Green’s function (results presented in Appendix B), the onset of voltage-driven alternans occurs at the same value as the onset of calcium-driven alternans, again up to a shift and scaling of $\eta$. Finally, in both the voltage-driven and calcium-driven cases, we find that waves are stationary (i.e., velocity $v = 0$) and the spatial wavelengths $\lambda_s$ agree.
Analysis of Discontinuous Alternans Profiles

In the previous chapter we studied the onset of alternans and the spatial properties of smooth wave profiles, in particular the spatial wavelength and velocity. We now move on to the second bifurcation $r_2(\Lambda)$ describing the transition from the smooth regime to the discontinuous regime and the dynamics of the discontinuous solutions themselves. We note that the discontinuous patterns found in the latter regime, as well and the bifurcation that leads to them, are not present in voltage-driven alternans. This is due to the fact that in the voltage-driven case, the instability driving alternans is effectively smoothed by the electrotonic coupling due to voltage diffusion. However, when alternans are calcium-driven, these two effects are separated so that there is no smoothness constraint on calcium profiles $c_n(x)$ due to the fact that no Green’s function appears in Equation (3.22).

Due to the discontinuities that form in the calcium profiles, solutions in this regime display a range of rich dynamics which we will study in this chapter. In the first section we will define some useful quantities and describe some basic properties of discontinuous profiles. In the second section we will study the bifurcation $r_2(\Lambda)$ using numerical techniques. In the third section we will describe how the shape of nodes changes as we change parameters. In the fourth section we will describe a unique hysteresis inherent to discontinuous profiles that we call unidirectional pinning. In the fifth section we will study more closely the dynamics of nodes and build a framework for understanding the mechanism behind unidirectional pinning. In the sixth section we will study the spatial scaling of solutions. Finally, in the seventh section we will show evidence that these results
generalize to the case of a more general form of nonlinearity in the single-cell calcium dynamics.

5.1 Properties of Discontinuous Solutions

We begin by defining, for each jump discontinuity in a steady-state calcium profile \( c(x) \), the right and left jumping points. Assuming that a discontinuous node occurs at \( x = x_0 \), we define \( c_- \) and \( c_+ \) to be the limiting values of \( c(x) \) as \( x \) approaches \( x_0 \) from the left and right, i.e.,

\[
c_-(x) = \lim_{x \to x_0^-} c(x),
\]

\[
c_+(x) = \lim_{x \to x_0^+} c(x).
\]

Additionally, we can use the definitions of the jumping points to define the total jump amplitude of a discontinuity. Since discontinuities occur at nodes, we have that at a given node the sign of \( c(x) \) switches, i.e., \( \text{sign}(c_-) = -\text{sign}(c_+) \). Thus, the total amplitude of a jump at a node \( x_0 \) is given by

\[
\text{total jump amplitude} = |c_+ - c_-|,
\]

where we take an absolute value to ensure a positive value. Due to the novelty of discontinuous patterns in this regime of solutions, as well as the physiological importance of nodes in cardiac tissue, we will be particularly interested in studying the dynamics of these discontinuous nodes, both in terms of their locations along the cable as well as the shape of the patterns around jump discontinuities.

In order to understand the nature of the transition between smooth and discontinuous patterns, we first present results from a numerical study where we compute the velocity \( v \) and total jump amplitude \( |c_+ - c_-| \) of steady-state solutions of Equations (3.22) and (3.23). We choose the asymmetry parameter \( w \) of the Green’s function to be zero so that smooth solutions have some finite velocity. Next, we fix \( \Lambda = 15 \) and simulate the system over a wide range of \( r \) values. Other parameters are \( \alpha, \gamma = \sqrt{0.3}, \beta = 0, \) and \( \xi = 1. \) For each \( r \) value we reset the cable to uniformly distributed noise about \( c_n(x) = 0 \) and \( a_n(x) = 0 \) and simulate ten thousand beats until steady-state to ensure that there are no hysteresis effects. In Figure 5.1 we plot the velocity \( v \) and total jump
amplitude $|c_+ - c_-|$ computed directly as a function of $r$. For smaller $r$ values the velocity $v$ is finite while the total jump amplitude $|c_+ - c_-| \approx 0$, indicating that solutions are smooth and there are no jump discontinuities. (We note that $|c_+ - c_-|$ is not exactly zero due to error inherent in the spatial discretization, but as we refine the spatial discretization, $\Delta x \to 0$, the total jump amplitude $|c_+ - c_-|$ approaches zero for these smaller $r$ values.) As $r$ increases, the velocity $v$ decreases in an approximately linear fashion until it vanishes at $r \approx 1.15$. This transition is the bifurcation $r_2(\Lambda)$, which we denote with a vertical dot-dashed green line. We also note that at exactly this point the total jump amplitude undergoes a discontinuous transition to a finite value, indicating that profiles have developed a discontinuity. Finally, as we continue to increase $r$ the velocity remains zero while the total jump amplitude $|c_+ - c_-|$ continues to increase smoothly along the black dashed curve, which we will discuss below.

![Figure 5.1](image_url)

Figure 5.1: The velocity $v$ and total jump amplitude $|c_+ - c_-|$ of steady state solutions computed from direct numerical simulation of Equations (3.22) and (3.23) plotted in blue circles and red dots, respectively, marking the transition from smooth to discontinuous patterns where velocity vanishes and total jump amplitude $|c_+ - c_-|$ jumps. After the transition the total jump amplitude $|c_+ - c_-|$ remains consistent with the theoretical prediction of Equation (5.7). Parameters used are $\Lambda = 15$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.

We seek to develop some intuition regarding the jumping values $c_-$ and $c_+$ as well as the total jump amplitude $|c_+ - c_-|$ in the discontinuous regime. Assuming period-two stationary solutions of the form $c(x) = c_n(x) = -c_{n+1}(x)$, which we insert into Equation (3.23), and taking a spatial
derivative, we find after some algebraic manipulation that
\[
\Lambda c'(x) = -\alpha \Lambda a'(x) - (r - 1)c(x) + c^3(x) \over r - 1 - 3c^2(x).
\] (5.4)

Upon inspection of the right-hand-side of Equation (5.4), we note that when \( c(x) \) attains the value \( \pm \sqrt{(r - 1)/3} \), the denominator vanishes, which causes the slope \( c'(x) \) to diverge and \( c(x) \) to develop a jump discontinuity. Thus, the left jumping point of a node is given by
\[
c_- = \pm \sqrt{(r - 1)/3}.
\] (5.5)

We can also compute the right jumping point \( c_+ \) by noting that, due to the smoothing effect of the Green’s function, the term \( A(x) = -\alpha a(x) + \frac{\alpha}{\Lambda} \int_{x}^{x'} e^{(x'-x)/\Lambda} a_0(x')dx' \) in Equation (3.22) remains smooth through the discontinuity so that \( \lim_{x \to x^-_0} d(x) = \lim_{x \to x^+_0} d(x) \). The quantity \( A(x_0) \) can be computed directly by evaluating Equation (3.22) at \( c(x) = \pm \sqrt{(r - 1)/3} \), yielding \( A(x_0) = \pm 2(r - 1)^{3/2}/3 \sqrt{3} \), and thus we can find the right jumping point \( c_+ \) simply by finding the other root of the cubic equation (where one solution is a double root), yielding
\[
c_+ = \mp 2\sqrt{(r - 1)/3}.
\] (5.6)

Having computed both jumping points \( c_- \) and \( c_+ \), we can now find the total jump amplitude, which is given by
\[
|c_+ - c_-| = \sqrt{3(r - 1)}.
\] (5.7)

In Figure 5.1 we plot the total jump amplitude given by Equation (5.7) in dashed black, noting that in the discontinuous regime \( r \geq r_2(\Lambda) \approx 1.15 \) the results from numerical simulation match up extremely well with the theoretical prediction.

For the rest of this chapter, we will refer to nodes with jumping points \( c_- = \pm \sqrt{(r - 1)/3} \) and \( c_+ = \mp 2\sqrt{(r - 1)/3} \) as normal jumps. Although profiles develop normal jumps when they first form, we will see that if parameters are changed after a discontinuous pattern has formed, the jumping points can change. In particular we will study the dynamics of the jumping points \( c_- \) and \( c_+ \) in the third section of this chapter.
5.2 Numerical Stability Analysis of Discontinuous Solutions

Thus far, analytical methods for finding an expression for the critical bifurcation value \( r_2(\Lambda) \) have proved fruitless. However, we can use numerical methods to study this bifurcation. To do this, we will study the stability of solutions in the discontinuous regime as we decrease \( r \) towards \( r_2(\Lambda) \) and into the smooth regime.

With this in mind, we assume a stationary discontinuous solution of the form \( c(x) = c_n(x) = -c_{n+1}(x) \) and study the evolution of a perturbation \( \delta c_n(x) \) to such a solution, where \( |\delta c_n(x)| \ll 1 \). For simplicity we will assume that the APD restitution parameter \( \beta \) and the asymmetry of the Green’s function \( w \) are both zero. Under these assumptions, Equations (3.22) and (3.23) can be combined into the single equation

\[
c_{n+1}(x) = -rc_n(x) + c_n^3(x) - \eta \int_0^L G(x' - x)c_n(x')dx' + \frac{\eta}{\Lambda} \int_0^x e^{\frac{x'-x}{\Lambda}} \int_0^L G(y - x')c_n(y)dydx',
\]

and the period-two solution \( c(x) \) satisfies

\[
(r - 1)c(x) = c^3(x) - \eta \int_0^L G(x' - x)c(x')dx' + \frac{\eta}{\Lambda} \int_0^x e^{\frac{x'-x}{\Lambda}} \int_0^L G(y - x')c(y)dydx.
\]

We now perturb the period-two solutions and consider solutions that evolve according to \( c_n(x) = (-1)^nc(x) + \delta c_n(x) \). Inserting this into Equation (5.8) and using Equation (5.9) to cancel terms, we obtain, after neglecting terms of order \( O(\delta c^2) \),

\[
\delta c_{n+1}(x) = [-r + 3c^2(x)]\delta c_n(x) - \eta \int_0^L G(x' - x)\delta c_n(x')dx' + \frac{\eta}{\Lambda} \int_0^x e^{\frac{x'-x}{\Lambda}} \int_0^L G(y - x')\delta c_n(y)dydx'.
\]

(5.10)

Our goal is to study the stability of the period-two solution \( c(x) \), so we are interested in the evolution of the perturbation \( \delta c_n(x) \). If this perturbation grows, then the solution \( c(x) \) is unstable, and if this perturbation decays, then the solution \( c(x) \) is stable. In order to study the evolution of the perturbation \( \delta c_n(x) \) numerically, we discretize the domain as \( \{x_i\}_{i=0}^{N} \), where \( x_i = i \frac{L}{N} = i\Delta x \). In order to represent functions as vectors and matrices, we modify our notation so that \( \delta c^n_i = \delta c_n(x_i) \),
\( \mathbf{c}_i = c(x_i) \), and \( G_{ij} = G(x_j - x_i) \). Thus, in vector form, Equation (5.10) can be rewritten as

\[
\delta \mathbf{c}^{n+1}_i = [ -r + 3c_i^2 ] \delta \mathbf{c}_i^n - \eta \left( \frac{L}{N} \right) \sum_{j=0}^{N} G_{ij} \delta \mathbf{c}_j^n + \frac{\eta}{\Lambda} \left( \frac{L}{N} \right)^2 \sum_{j=0}^{i} e^{-x_j/\Lambda} \left( \sum_{k=0}^{N} G_{jk} \delta \mathbf{c}_k^n \right). \tag{5.11}
\]

Equation (5.11) can be rewritten as the simple matrix equation

\[
\delta \mathbf{c}^{n+1} = A \delta \mathbf{c}^n, \tag{5.12}
\]

where the matrix \( A \) is defined as

\[
A_{ij} = ( -r + 3c_i^2 ) \delta_{ij} - \eta \left( \frac{L}{N} \right) G_{ij} + e^{-x_i/\Lambda} \frac{\eta}{\Lambda} \left( \frac{L}{N} \right)^2 \sum_{k=0}^{i} e^{x_k/\Lambda} G_{k,j}. \tag{5.13}
\]

Given a period-two solution \( c(x) \) obtained numerically, we can then build the matrix \( A \) from Equation (5.13) and study the evolution of \( \delta \mathbf{c}^n \) using the spectrum of \( A \). If all eigenvalues of \( A \) are less than unity, i.e., \( |\lambda| < 1 \) for all \( \lambda \in \sigma(A) \), then the perturbation \( \delta \mathbf{c}^n \) will decay along every eigendirection of \( A \) and \( \delta \mathbf{c}^n \to 0 \) as \( n \to \infty \), indicating that \( c(x) \) is linearly stable. On the other hand, if there is one or more eigenvalues \( \lambda \in \sigma(A) \) such that \( |\lambda| > 1 \), then the perturbation \( \delta \mathbf{c}^n \) will grow along each eigendirection associated with an eigenvalue greater than unity, indicating that the period-two solution \( c(x) \) is linearly unstable.

We finish our numerical stability analysis by building a branch of discontinuous, stationary period-two solutions from which we can compute for each solution the matrix \( A \) and its spectrum. To do this, we start from a stable period-two solution in the discontinuous regime and continue the branch into the smooth regime by using Newton’s method to solve Equation (5.9) for various values of \( r \). Fixing \( \Lambda = 15, \alpha, \beta = \sqrt{0.3}, \beta = 0, \xi = 1, \) and \( w = 0 \), for each value of \( r \) we obtain a discontinuous, stationary period-two solution and compute the dominant eigenvalue \( \lambda_A \) (i.e., the eigenvalue of maximum magnitude) of the corresponding matrix \( A \). In Figure (5.2) we plot the resulting eigenvalue \( \lambda_A \) (blue circles) as a function of \( r \), which we start at \( r = 1.15 \) and decreased until the Newton iteration no longer converges. As \( \lambda_A \) is real and negative (corresponding to stationary period-two solutions) we denote \(-1\) with a dashed red line. We see that \( |\lambda_A| < 1 \) for larger \( r \) values until \( r \approx 1.135 \) at which point \( \lambda_A \) crosses unity, indicating that the discontinuous solution loses stability at a value \( r \) that is consistent with the results in Figure 5.1.
Figure 5.2: The dominant eigenvalue $\lambda_A$ of the matrix $A$ from Equation (5.13) governing the stability of discontinuous, stationary, period-two solutions $c(x)$. Parameters used are $\Lambda = 15$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.

5.3 Shape of Calcium Profiles Around Nodes

Having studied the basic properties of discontinuous patterns and the bifurcation $r_2(\Lambda)$ in the previous section, we now turn to study the rich dynamics of these profiles under changes of parameters. We start by considering the shape of steady-state discontinuous profiles $c(x)$ about a node. As we discussed in the first section, upon formation, discontinuous patterns typically form normal jumps, where the jumping values $c_-$ and $c_+$ are given by $\pm \sqrt{(r-1)/3}$ and $\mp 2\sqrt{(r-1)/3}$, respectively. Because the profile $c(x)$ has no local symmetry, i.e., $c_+ \neq -c_-$, we say that the shape of the calcium profile around nodes whose jumps are normal is asymmetric.

However, we find that if either of the parameters $r$ or $\Lambda$ are changed, then the shape of the calcium profiles around the nodes, e.g., the jumping points $c_-$ and $c_+$, change. In particular, if either $r$ or $\Lambda$ are increased after a discontinuous solution is formed, then the resulting $|c_-|$ and $|c_+|$ values are found to be greater than and less than, respectively, the values described by a normal jump. In fact, we find that as we increase $r$ or $\Lambda$ the values $|c_-|$ and $|c_+|$ approach one another. This is easiest to see when we keep $r$ constant while changing $\Lambda$, since $\Lambda$ can be increased without bound and $r$ affects the original jumping point values for a normal jump.

To describe the shape of nodes, we introduce a measure of asymmetry $\Delta$ for each node,
defined by
\[ \Delta \equiv \frac{|c_+| - |c_-|}{\sqrt{(r-1)/3}}, \]  
(5.14)

where we normalize by \( \sqrt{(r-1)/3} \) so that the maximum value of \( \Delta = 1 \) is attained at a normal jump. We investigate how the shape of the calcium profile around nodes changes by fixing \( r = 1.2, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \) and \( w = 0, \) obtaining a stationary discontinuous solution for \( \Lambda = 12, \) and then tracking the jumping points \( c_- \) and \( c_+ \) along with the asymmetry \( \Delta \) as we increase \( \Lambda \).

In Figure 5.3 we plot the resulting values of \( |c_-|, |c_+|, \) and \( \Delta \) as a function of \( \Lambda \). We see that as \( \Lambda \to \infty, |c_-| \) and \( |c_+| \) tend towards one another. In fact, it can be shown that when the asymmetry length scale \( w \) is zero, i.e., the Green’s function \( G \) is symmetric, both \( |c_-| \) and \( |c_+| \) tend towards the value \( \sqrt{r-1} \), which is denoted as the horizontal dashed black line. This limiting value is calculated in Chapter 7, where we study the dynamics of the system given by Equation (3.22) and (3.23) in the \( \Lambda \to \infty \) limit corresponding to a flat CV restitution curve. Furthermore, we see that the asymmetry \( \Delta \) quickly decays and approaches zero as \( \Lambda \to \infty \). We also note that if \( \Lambda \) is decreased back to its original value, the shape of the calcium profile around the node recovers the properties of a normal jump.

Figure 5.3: Behavior of jumping values \( c_- \) and \( c_+ \) as well as the asymmetry \( \Delta \) as a result of increasing \( \Lambda \). Parameters used are \( r = 1.2, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \) and \( w = 0. \)

We note briefly that when the asymmetry \( w \) is non-zero the limiting points of \( |c_-| \) and \( |c_+| \) as \( \Lambda \to \infty \) are no longer equal. In fact, it can be shown that in this limit \( c_- \) surpasses \( c_+ \) in
absolute value, yielding a negative value of $\Delta$ for large enough $\Lambda$. In Chapter 7 we will discuss this phenomenon in more detail.

### 5.4 Unidirectional Pinning and Hysteresis

In the previous section we described how the shape of $c(x)$ around the nodes, in particular the jumping points $c_-$ and $c_+$, change as $r$ and $\Lambda$ are increased, and how this causes the local asymmetry $\Delta$ of the nodes to change. We also note that when $r$ or $\Lambda$ are increased in these scenarios, then the location of the nodes do not change. We now consider decreasing either $r$ or $\Lambda$ and studying the effect this has on the nodes of $c(x)$. While increasing $r$ or $\Lambda$ caused the shape of the nodes to change, but not the locations, we find that decreasing $r$ or $\Lambda$ in fact has the opposite effect: the locations of the nodes change but the shape of the nodes remains the same.

Starting from a period-two solution of Equations (3.22) and (3.23) in the discontinuous regime with normal jumps, we find that if either $r$ or $\Lambda$ are decreased (and remain in the discontinuous regime), then the locations of the nodes move towards the pacing site at $x = 0$ until the profile has converged to another steady-state period-two solution. Furthermore, while the locations of the nodes are closer to the pacing site in the new profile, each node is a normal jump, i.e., the local shape of the nodes is conserved after the shift. However, if we restore $r$ or $\Lambda$ to their original values by increasing them, then the nodes do not move back to their original positions. Instead, the node locations remain constant while the shape of the nodes changes in a manner consistent with the dynamics described in the previous section. These properties show that memory is very important to solutions in the discontinuous regime, and these solutions display a unique hysteresis. Furthermore, since the locations of nodes can be moved towards, but not away from, the pacing site, we call this phenomena unidirectional pinning. We discuss the physiological implications of unidirectional pinning in Chapter 8.

We now illustrate the phenomenon of unidirectional pinning. First we obtain a steady-state period-two discontinuous solution by direct simulation of Equations (3.22) and (3.23) using parameters $r = 1.2$, $\Lambda = 17$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$. Next, we slowly change $\Lambda$ in a
“zig-zag” fashion and track the location of the first node, denoted $x_1$. First, we increase $\Lambda$ to 20, then decrease it to 10, then increase it again to 13. In Figure 5.4 we present the results, plotting the location of the first node $x_1$ in blue circles and the value of $\Lambda$ as a dashed red curve. We note that as we initially increase $\Lambda$, $x_1$ remains constant. The node only moves when we decrease $\Lambda$ below its previous minimum of 17, at which point $x_1$ moves towards the pacing site, scaling linearly with $\Lambda$. Finally, when we increase $\Lambda$ towards the end, $x_1$ remains constant, signifying that the node remains pinned.

![Figure 5.4: Location of the first node $x_1$ as $\Lambda$ is slowly changed. Parameters used are $r = 1.2$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.](image)

We now generalize these results by presenting an example that illustrates the hysteresis of both the shape and pinning of nodes in the solutions in the discontinuous regime. Furthermore, we will show that changing $r$ has a qualitatively similar effect of the nodes as changing $\Lambda$. We choose two points in $(r, \Lambda)$ parameter space: a start point $(r_1, \Lambda_1) = (1.16, 30)$ and an end point $(r_2, \Lambda_2) = (1.26, 14)$. We next define two paths connecting $(r_1, \Lambda_1)$ to $(r_2, \Lambda_2)$. The first we denote Path 1, which is given by first increasing $r$ from $r_1$ to $r_2$ while $\Lambda$ remains constant at $\Lambda_1$, then decreasing $\Lambda$ from $\Lambda_1$ to $\Lambda_2$ while $r$ remains constant at $r_2$. The second we denote Path 2, which is essentially the opposite of Path 1, given by first decreasing $\Lambda$ from $\Lambda_1$ to $\Lambda_2$ while $r$ remains constant at $r_1$, then increasing $r$ from $r_1$ to $r_2$ while $\Lambda$ remains constant at $\Lambda_2$ (See Figure 5.5). Next, after obtaining a steady-state period-two solution at $(r_1, \Lambda_1)$ we move slowly along Paths 1
and 2 in different simulations, tracking both the asymmetry $\Delta$ and the location of the first node $x_1$ along each path. Other parameters in the simulation are $\alpha, \gamma = 0.3$, $\beta = 0$, $\xi = 1$, and $w = 0$.

In the first panel of Figure 5.5 we plot Paths 1 and 2 in $(r, \Lambda)$ space, denoting the start and end points by black circles and Paths 1 and 2 in blue and red, respectively. In the second panel we plot a zoom-in on the first node of the initial steady-state profile $c_0(x)$ obtained at $(r_1, \Lambda_2)$ in black, as well as the end profiles $c_1(x)$ (blue) and $c_2(x)$ (red) obtained after slowly moving along Paths 1 and 2, respectively, ending up at $(r_2, \Lambda_2)$. Of particular interest is that, despite the ending profiles $c_1(x)$ and $c_2(x)$ having the same exact parameters, their properties are very different. The first profile $c_1(x)$ is very similar to the initial profile $c_0(x)$, where in fact the location of the first node is exactly the same, and the shape of the node is only slightly different. The second profile $c_2(x)$, on the other hand, looks very different, having changed greatly from the initial profile $c_0(x)$. Most notably, the location of the first node is much closer to the pacing site, while the shape is also much more symmetric than either that of $c_0(x)$ or $c_1(x)$.

![Figure 5.5: Paths 1 and 2 through $(r, \Lambda)$ parameter space, along with the initial profile $c_0(x)$ (black) along with ending profiles $c_1(x)$ (blue) and $c_2(x)$ (red) obtained from moving along Paths 1 and 2, respectively. Parameters used are $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.](image)

Furthermore, we also track the asymmetry $\Delta$ and location of the first node $x_1$ along both Paths 1 and 2, which we plot in Figure 5.6. We plot the asymmetry $\Delta$ (blue circles) and first node
location \( x_1 \) (red crosses) along Paths 1 and 2 in the first and second panels, respectively. Along the first segment of Path 1, the asymmetry first decreases, but increases along the second segment until it is almost restored to one, while the location of the first node remains constant throughout all of Path 1. Along the first segment of Path 2 the asymmetry remains approximately constant while the first node moves in towards the pacing site, then along the second segment the asymmetry decreases while the node remains pinned. Although the start and end parameter values along both Paths are identical, Figure 5.6 highlights the hysteresis affecting solutions in the discontinuous regime, since the resulting asymmetries \( \Delta \) and first node locations are completely different.

![Figure 5.6: Evolution of the asymmetry \( \Delta \) and first node location \( x_1 \) along Paths 1 and 2. Parameters used are \( \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \) and \( w = 0. \)](image)

5.5 Analysis of Node Dynamics

Due to the novel hysteretic properties of solutions in the discontinuous regime, we now study in more detail the dynamics of the nodes and jumping points in order to build a stronger framework for understanding phenomena like unidirectional pinning. Recall that by defining \( A_n(x) = -\alpha a_n(x) + \frac{\alpha}{\Lambda} \int_0^x e^{(x'-x)/\Lambda}a_n(x')dx' \), Equation (3.22) can be rewritten as

\[
 c_{n+1}(x) = -rc_n(x) + c_n^3(x) + A_n(x),
\]  
(5.15)
where the term $A_n(x)$ now includes all the nonlocal effects for the evolution of $c_n(x)$. Previously we found that for a steady-state solution $-c_{n+1}(x) = c_n(x) = c(x)$ with a normal jump at $x = x_0$, the values of the jumping points $c_-$ and $c_+$ are exactly the roots of

$$F(c) = (r - 1)c - c^3 - A = 0,$$ (5.16)

where $A = \pm 2(r - 1)^{3/2}/3\sqrt{3}$. Without any loss of generality, we will assume the positive value of $A$, which yield the combination of jumping points $c_- = \sqrt{(r - 1)/3}$ and $c_+ = -2\sqrt{(r - 1)/3}$.

In Figure 5.7 we plot the polynomial $F(c) = (r - 1)c - c^3 - A$ for $r = 1.2$ and plot the jumping points $c_-$ and $c_+$, given by roots of $F(c)$, in a red circle and green cross. In particular, we note that the jumping point $c_-$ is given by a double root of $F(c)$, which we will see is essential to unidirectional pinning. Next, at a given node we define the quantity $\Delta c_{n+1} = (-c_{n+1}) - c_n$, which represents, after accounting for the flip in sign of $c_{n+1}$, the evolution of $c$ along one beat. By evaluating Equation (5.15) at $x = x_0$, we find that

$$\Delta c_{n+1} = (r - 1)c_n - c_n^3 - A = F(c_n),$$ (5.17)

from which we can deduce the evolution and thus the stability of each jumping point. We find that, assuming $c_- = \sqrt{(r - 1)/3}$ and $c_+ = -2\sqrt{(r - 1)/3}$, $\Delta c_{n+1} < 0$ for $c_n > c_+$ and $\Delta c_{n+1} > 0$ for $c_n < c_+$. We illustrate this in Figure 5.7 by denoting the direction of evolution between each solution with arrows. While $c_+$ is stable from above and below, $c_-$ is only semi-stable: stable from above, but unstable from below. Thus, the value $c_-$ at a normal jump is unstable to perturbations in the negative direction, a direct consequence of the double multiplicity of the root at $c_-$. 

We next consider the effects of changing parameters after a normal jump is achieved. Since all non-local effects on the dynamics of $c_n(x)$ in Equation (5.15) are captured by $A_n(x)$, we argue that the immediate effects of a change in parameters will primarily be on $A$. Furthermore, since $A$ is defined as an integral, the value of $c(x)$ at a particular point $x = x_0$ has no effect on $A$. Therefore, we will study the dynamics of $c$ in response to changes of $A$, in particular the dynamics of $c_-$ and $c_+$. For a given value of $A$, the steady-state values $c_-$ and $c_+$ are again given by the roots of Equation (5.16) and the dynamics are described by Equation (5.17).
Figure 5.7: Jumping point dynamics of $c_-$ and $c_+$ for a normal jump, plotted as a red circle and green cross, respectively, given by the roots of $F(c) = (r - 1)c - c^3 - A$ for $r = 1.2$.

In Figure 5.8 we now illustrate the effect of a decrease and increase in $A$. In the first panel we see that a decrease in $A$ causes an upward shift in $F(c)$. This causes the root $c_+$ to increase, i.e., moving in towards zero, while the double root $c_-$ splits into two distinct roots. By Equation (5.17) we deduce that the lesser of these roots is unstable, so that the stable root representing $c_-$ increases. Thus a decrease in $A$ causes an increase and decrease, respectively, in the magnitudes $|c_-|$ and $|c_+|$. Since neither root $c_-$ or $c_+$ disappears, in terms of a profile with a node at $x = x_0$, this implies that the node will remain at $x_0$. However, the asymmetry, as measured by the difference in the magnitudes of $c_-$ and $c_+$ will decrease.

In the second panel, we see that an increase in $A$ causes a downward shift in $F(c)$. While this causes the root $c_+$ to decrease, the double root $c_-$ disappears entirely, owing to the quadratic multiplicity of the root. Since $\Delta c < 0$ for any $c > c_+$, this implies that the point $c_-$ decays to $c_+$, representing a shift in the point $c(x_0)$ from $c_-$ to $c_+$, thus causing the node to move in the negative direction, i.e., towards $x = 0$. As we have seen, after movement towards the pacing site, a normal jump then forms at a new point closer to $x_0$, which in turn cannot be moved away from $x = 0$ according to the explanation above.

Alternatively, this problem can be studied using the framework of a gradient system with an energy potential [48, 57, 59]. Since the beat-to-beat dynamics of alternans in cardiac tissue evolve
Figure 5.8: Jumping point dynamics of $c_-$ and $c_+$ after parameters are changed from a normal jump, plotted as a red circle and green cross, respectively, given by the roots of $F(c) = (r - 1)c - c^3 - A$ for $r = 1.2$. In the first and second panel, respectively, the results from decreasing and increasing $A$.

very slowly (e.g. steady-state profiles are only reached after a transient of several thousands of beats), discrete beat-to-beat differences can be approximated by continuous-time derivatives, i.e., the quantity $\Delta c_{n+1}$ in Equation (5.17) can be replaced with the derivative $dc/dt$, where $t$ is in units of beats. Therefore, Equation (5.17) can be rewritten as

$$\frac{dc}{dt} = -\frac{d}{dc} V(c),$$

(5.18)

where $V(c)$ describes the potential energy well given by

$$V(c) = -\frac{(r - 1)c^2}{2} + \frac{c^4}{4} + Ac + K,$$

(5.19)

for any constant $K$. By defining energy $E = V(c)$ we find that the time-derivative of the energy is

$$\frac{d}{dt} E = \frac{d}{dc} V(c) \cdot \frac{dc}{dt} = -\left(\frac{dc}{dt}\right)^2,$$

(5.21)

i.e., the energy is always decreasing. Thus, steady-state jumping point solutions are given by the flat points of the potential energy landscape $V(c)$. Furthermore, valleys and peaks of $V(c)$ represent stable and unstable solutions, respectively.

In Figure 5.9 we plot the potential energy well $V(c)$ with jumping points $c_-$ and $c_+$ as a red circle and green cross, respectively, for a normal jump with $r = 1.2$. We note that the equilibrium
representing $c_+$ is a true minimum, and thus stable to perturbation in both directions, while the equilibrium representing $c_-$ is not a true minimum. Mathematically, this is reflected in the fact that the second derivative $V''(c)$ vanishes at $c = c_-$, and from the shape of $V(c)$ we can see that $c_-$ is stable to perturbations in the positive direction, but unstable to perturbations in the negative direction, matching up with our theory above.

![Figure 5.9: Jumping points $c_-$ and $c_+$, plotted as a red circle and green cross, respectively, represented as the equilibria of the potential well $V(c)$ for a normal jump using $r = 1.2$.](image)

Next, we explore the effect that changing $A$ has on the potential energy well $V(c)$. In Figure 5.10 we plot for $r = 1.2$ the potential energy well $V(c)$ with jumping points $c_-$ and $c_+$ as a red circle and green cross, respectively, after decreasing and increasing $A$ from a normal jump in the first and second panels, respectively. When $A$ is decreased, we find that the equilibrium representing $c_+$ remains a true minimum, while the equilibrium representing $c_-$ changes to a true minimum as well, implying that both jumping points are stable to perturbations in both directions. When $A$ is increased, on the other hand, we find that the equilibrium representing $c_-$ vanishes due to the increased slope induced by the $Ac$ term in Equation (5.19). Thus, a decrease in $A$ will yield no movement of the node, while an increase in $A$ will cause a point $c(x_0) = c_-$ to “roll down” the landscape described by $V(c)$, effectively switching to $c_+$ and causing the node to move towards the pacing site.

The analysis presented above provides a framework for explaining unidirectional pinning via changes in the value of $A = A(x_0)$. To finish the analysis, we now connect changes in $A$ with explicit
In Table 5.1 we present the results from numerically calculating the derivative of $A$ with respect to $\Lambda$ and $r$, as well as $\alpha$, $\beta$, and $\gamma$ at a normal jump with parameter values $r = 1.2$, $\Lambda = 15$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$. In particular, both $\partial A/\partial \Lambda$ and $\partial A/\partial r$ are negative, implying that a decrease in $\Lambda$ or $r$ causes nodes to move towards the pacing site and an increase in $\Lambda$ or $r$ causes the nodes to remain stationary but decrease their asymmetry. Recall that this is in agreement to results presented previously in this Chapter. We also find the derivatives $\partial A/\partial \alpha$, $\partial A/\partial \beta$, and $\partial A/\partial \gamma$ to be positive, implying that increasing $\alpha$, $\beta$, or $\gamma$ causes node locations to
move towards the pacing site, while decreasing them causes nodes to remain stationary and decrease their asymmetry. We also find this to be in agreement with numerical experiments. We note that for different parameter values these derivatives change, but preserve their sign over all parameter values we have tested. Thus, the effect that changing a given parameter in a given direction has on nodes with normal jumps remains qualitatively the same throughout parameter space.

<table>
<thead>
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<th>Derivative value</th>
<th>(\partial A/\partial \Lambda)</th>
<th>(\partial A/\partial r)</th>
<th>(\partial A/\partial \alpha)</th>
<th>(\partial A/\partial \beta)</th>
<th>(\partial A/\partial \gamma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.00232418</td>
<td>-0.0281439</td>
<td>0.0462741</td>
<td>0.0769836</td>
<td>0.10796</td>
</tr>
</tbody>
</table>

Table 5.1: Numerically computed derivatives of \(A\) with respect to different parameters for \(r = 1.2, \Lambda = 15, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, w = 0\).

### 5.6 Scaling of Node Locations and Spatial Wavelength

We next consider the scaling of node location in discontinuous solutions, or equivalently the spatial wavelength of profiles. As we saw in the previous section, node locations become pinned towards the pacing site when parameters are changed, so the wavelength of a particular solution is the minimum wavelength dictated by the parameter history of that solution. In particular, we will focus on how the node locations vary according to the CV restitution parameter \(\Lambda\).

Upon inspection of Figure 5.4, in particular the middle portion where the first node location \(x_1\) decreases as we decrease \(\Lambda\), it appears that the location of the first node scales linearly with \(\Lambda\). We investigate this further by tracking the location of the first node \(x_1\) over a much larger range of \(\Lambda\) values. In Figure 5.11 we plot the first node location \(x_1\) as a function of \(\Lambda\) in blue circles as we decrease \(\Lambda\) from 100 to 10. Other parameters used are \(r = 1.2, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, w = 0\). Using linear least squares, we find that \(x_1 \approx 1.14 + 0.12\Lambda\) represents the results very well, confirming that the first node location scales linearly with \(\Lambda\). To guide the eye, we plot a short line of slope 0.12 in dashed black.

We also investigate the spatial wavelength \(\lambda_s\) of profiles, defined as twice the average distance between two adjacent nodes. We compute the spatial wavelength \(\lambda_s\) over the same range of \(\Lambda\) values and plot the results (red crosses) in Figure 5.12. Other parameters used are \(r = 1.2, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, w = 0\).
Figure 5.11: Location of the first node $x_1$ as a function of $\Lambda$. Results are well described by $x_1 \approx 1.14 + 0.12\Lambda$. Parameters used are $r = 1.2$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.

$\beta = 0$, $\xi = 1$, and $w = 0$. Again, we use linear least squares to find the line of best fit and find that $\lambda_s \approx 4.00 + 0.45\Lambda$ fits the results very well, confirming that the spatial wavelength $\lambda_s$ also scales linearly with $\Lambda$. To guide the eye, we plot a short line of slope 0.45 in dashed black.

To explain this phenomenon of linear spatial scaling with $\Lambda$ in the discontinuous regime, we revisit Equation (5.4), which we obtained by assuming steady-state period-two solutions $-c_{n+1}(x) = c_n(x) = c(x)$ and $-a_{n+1}(x) = a_n(x) = a(x)$ of Equation (3.22) and differentiating with respect to $x$. If, instead, we take a derivative with respect to the scaled spatial variable $y = x/\Lambda$, then $dc/dx = \Lambda^{-1}dc/dy$ and $da/dx = \Lambda^{-1}da/dy$. Finally, if we define the new functions $\tilde{c}(y) = c(\Lambda y)$ and $\tilde{a}(y) = a(\Lambda y)$, we obtain a new differential equation

$$
\tilde{c}'(y) = \frac{-\alpha\tilde{a}'(y) - (r - 1)\tilde{c}(y) + \tilde{c}^3(y)}{r - 1 - 3\tilde{c}^2(y)},
$$

(5.22)

where $'$ now denotes differentiation with respect to $y = x/\Lambda$. Equation (5.22) governs the shape of $\tilde{c}(y)$ inside each half-wavelength and has some intrinsic wavelength $\tilde{\lambda}_s$ that depends on the other parameters $r$, $\alpha$, $\gamma$, $\beta$, $\xi$ and $w$, but not $\Lambda$. Thus, converting back to $x = \Lambda y$, we have that $\lambda_s = \Lambda\tilde{\lambda}_s$. We therefore argue that the wavelength of discontinuous solutions scale linearly with $\Lambda$ plus a sub-dominant correction of order $\xi$ that accounts for the steep portions of $c(x)$ profiles very near the nodes.

Another approach to describing the spatial scaling of solutions in the discontinuous regime
is to derive an ODE that approximates the shape of profiles (away from the discontinuities). Note that by dropping the $\sim$-notation and replacing $y$ with $x$ in Equation (5.22) yields

$$[r - 1 - 3c^2(x)]c'(x) + \alpha a'(x) = c^3(x) - (r - 1)c(x),$$

(5.23)

which is a differential equation involving two different functions. The ODE approach involves approximating $a(x)$ in terms of $c(x)$ using Equation (3.23) so that the $a'(x)$ term can be eliminated from Equation (5.23), yielding a single ODE for a single function $c(x)$. Unfortunately, the resulting ODE is difficult to treat analytically, yielding only numerical results that shed no more light on the analytical description of the spatial scaling of solutions. We forgo presenting the analysis of this ODE approach here, but include it in Appendix C for completeness.

### 5.7 General Nonlinearities in Single-Cell Calcium Dynamics

We conclude this chapter by discussing how some of the results presented above generalize to the case of a more general nonlinearity in the single-cell calcium dynamics. Recall that this is equivalent to replacing the cubic $c^3_n(x)$ in Equation (3.22) with the more general $f[c_n(x)]$, where

$$f(c) = gc^3 + \chi_1 c^5 + \cdots + \chi_m c^{2m+3}.$$  

(5.24)

We begin by presenting an example of a discontinuous steady-state solution after replacing
the cubic term \( c_n^3(x) \) in Equations (3.22) and (3.23) with the quintic term

\[
f(c) = gc^3 + \chi c^5.
\]  

(5.25)

In Figure 5.13 we plot the calcium and voltage profiles \( c(x) \) and \( a(x) \) using parameters \( r = 1.2, \Lambda = 15, \alpha, \beta = \sqrt{0.3}, \beta = 0, \xi = 1, w = 0, g = 0.6, \) and \( \chi = 0.4 \). Comparing Figure 5.13 to Figure 3.3, it is clear that introducing higher-order nonlinearities into Equation (3.22) do not qualitatively change the resulting profiles.

![Figure 5.13: A discontinuous alternans solution \( c(x) \) and \( a(x) \) of Equations (3.22) and (3.23), where the cubic term is replaced by the quintic \( gc_n^3(x) + \chi c_n^5(x) \). Parameters are \( r = 1.2, \Lambda = 15, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, w = 0, g = 0.6, \) and \( \chi = 0.4 \).](image)

Next, we consider the values and behavior of jumping points at each node. As we did previously, we assume stationary period-two solutions of the form \( -c_{n+1}(x) = c_n(x) = c(x) \) and \( -a_{n+1}(x) = a_n(x) = a(x) \), and after taking a derivative with respect to \( x \), we find that Equation (5.4) becomes

\[
\Lambda c'(x) = -\alpha \Lambda a'(x) - (r - 1)c(x) + f[c(x)] \quad r - 1 - f'(c(x)).
\]  

(5.26)

Thus, from Equation (5.26) we can find the values of jumping points \( c_- \) and \( c_+ \) by finding when the denominator vanishes, causing \( c'(x) \) to become unbounded at \( x = x_0 \) and to form a jump discontinuity. Thus, the value of \( c_- \) is given by solving

\[
f'(c_-) = r - 1.
\]  

(5.27)
We note that when \( f(c) \) is quintic, then \( f'(c) \) is quartic and \( c_- \) can be found analytically, but when \( f(c) \) is seventh-order or higher \( c_- \) needs to be found numerically. As before, the quantity

\[
A(x) = -\alpha a(x) + \frac{2}{\Lambda} \int_0^x e^{(x'-x)/\Lambda}a(x')dx'
\]

remains smooth through the discontinuity at \( x = x_0 \), so that after finding \( A(x_0) = (r - 1)c_- - f(c_-) \), the second jumping point \( c_+ \) can be found by finding the other roots of

\[
(r - 1)c_+ - f(c_+) = d(x_0).
\]

The jumping points \( c_- \) and \( c_+ \) described above form initially when discontinuous patterns spontaneously form in tissue, constituting normal jumps for a general nonlinearity \( f(c) \), which we denote by \( c_{-,0} \) and \( c_{+,0} \). Furthermore, we find that the behavior of \( c_- \) and \( c_+ \) in response to an increase in \( r \) or \( \Lambda \) is similar to that of a cubic nonlinearity. In other words, we find that, for instance, in the limit of large \( \Lambda \), the jumping points \( c_- \) and \( c_+ \) approach one another in magnitude. Furthermore, the generalized measure of asymmetry

\[
\Delta = \frac{|c_+| - |c_-|}{|c_{+,0}| - |c_{-,0}|}
\]

approaches zero. In Figure 5.14 we confirm these results by plotting the evolution of \( |c_-| \), \( |c_+| \), and \( \Delta \) as \( \Lambda \) is increased after a discontinuous pattern is formed at \( \Lambda = 10 \), for a quintic nonlinearity. Other parameters are \( r = 1.2 \), \( \alpha, \gamma = \sqrt{0.3} \), \( \beta = 0 \), \( \xi = 1 \), \( w = 0 \), \( g = 0.6 \), and \( \chi = 0.4 \).

![Figure 5.14: Behavior of jumping values \( c_- \) and \( c_+ \) as well as the asymmetry \( \Delta \) as a result of increasing \( \Lambda \) for a quintic nonlinearity. Parameters used are \( r = 1.2 \), \( \alpha, \gamma = \sqrt{0.3} \), \( \beta = 0 \), \( \xi = 1 \), \( w = 0 \), \( g = 0.6 \), and \( \chi = 0.4 \).](image_url)

First, we see in Figure 5.14 that although \( |c_-| \) and \( |c_+| \) take on slightly larger values than...
those for a cubic nonlinearity, they approach one another in the same way and $\Delta \to 0$, similar to Figure 5.3. Additionally, we calculate the initial jumping points $|c_{-,0}|$ and $|c_{+,0}|$ using the method outlined above, finding numerically that $|c_{-,0}| = 0.32$ and $|c_{+,0}| = 0.60$. In Figure 5.14 we plot these values with black circles, noting that they match up very well with simulations. We also note that unlike the results for a cubic nonlinearity, the magnitude of the jumping point on the positive side of the discontinuity is not twice the magnitude of the jumping point on the negative side of the discontinuity, i.e., $|c_{+,0}| \neq 2|c_{-,0}|$. Finally, we can also calculate the value towards which $|c_-|$ and $|c_+|$ approach using a method we describe in Chapter 7. This value is given in general by the solution of

$$
\frac{f(c_{+/})}{c_{+/}} = r - 1,
$$

which in the case of a quintic nonlinearity given by Equation (5.25) yields

$$
c_- = \pm \sqrt{-3g + \sqrt{9g^2 + 20\chi(r-1)}}
$$

$$
c_+ = \mp \sqrt{-g + \sqrt{g^2 + 4\chi(r-1)}}.
$$

We plot this value in Figure 5.14 in dashed black, noting that it describes the limiting values very accurately.

Figure 5.15: Location of the first node $x_1$ as $\Lambda$ is slowly changed for a quintic nonlinearity. Parameters used are $r = 1.2$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, $w = 0$, $g = 0.6$, and $\chi = 0.4$.

Next, we show that unidirectional pinning still occurs in cases of more general nonlinearity.
We again assume a quintic nonlinearity given by Equation (5.25), and after obtaining a steady-state discontinuous profile, zig-zag $\Lambda$ in the same way as we did previously, increasing $\Lambda$ from 16 to 20, then decreasing it to 10, then increasing it to 14. We present our results in Figure 5.15, plotting the first node location $x_1$ in blue circles and $\Lambda$ in dashed red. Other parameters are $r = 1.2$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, $w = 0$, $g = 0.6$, and $\chi = 0.4$. We primarily note that, although the first node locations $x_1$ are slightly higher with our particular choice of $f(c)$ compared to the cubic, the behavior is qualitatively the same as in Figure 5.4, confirming that unidirectional pinning occurs with more general nonlinearities. We also note that the node dynamics analysis that explains the hysteresis found in discontinuous solutions can be generalized to more general nonlinearities as well.

Finally, we close by remarking on the scaling of discontinuous solutions with more general nonlinearities. Revisiting Equation (5.26) we can see that only $c'(x)$ and $a'(x)$ are multiplied by $\Lambda$. As before, $\Lambda$ can be scaled out of this equation simply by rescaling space by $\Lambda$. Thus, we expect the node locations and wavelength of solutions to scale linearly with $\Lambda$ for the case of a general nonlinearity, as they do with a cubic. In Figure 5.16 we present results confirming this hypothesis, plotting the first node location $x_1$ and spatial wavelength $\lambda_s$ as a function of $\Lambda$ for a quintic nonlinearity given by Equation (5.25). Other parameters are $r = 1.2$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, $w = 0$, $g = 0.6$, and $\chi = 0.4$. Clearly both the first node location and spatial wavelength are slightly larger for our choice of $f(c)$, however both scale linearly with $\Lambda$ as we expect. Results are well described by $x_1 \approx 1.11 + 0.15\Lambda$ and $\lambda_s \approx 3.06 + 0.58\Lambda$. 
Figure 5.16: Location of the first node location $x_1$ and spatial wavelength $\lambda_s$ as a function of $\Lambda$ for a quintic nonlinearity. Parameters used are $r = 1.2$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, $w = 0$, $g = 0.6$, and $\chi = 0.4$. 
Chapter 6

Numerical Experiments of Detailed Ionic Models

In Chapter 3 of this Thesis we derived a reduced system governing the dynamics of calcium-driven alternans in a cable of tissue, given by Equations (3.22) and (3.23), and in Chapters 4 and 5 analytically and numerically studied this system. Having developed a solid understanding of the dynamics of this system, we now return to the ionic model presented in Chapter 2 to connect the findings of our reduced model to more detailed models. In particular, we now present several numerical experiments to confirm that the dynamics of our reduced model can be observed in detailed ionic models. Furthermore, we also show that in addition to these qualitative predictions, we can in fact quantitatively predict behavior in detailed ionic models using our reduced model.

In the first section, because the CV restitution length scale $\Lambda$ is so important in the dynamics of the reduced model, we show that we can numerically compute it from the CV restitution curves first presented in Chapter 2. In the second section, due to the novelty of unidirectional pinning in the discontinuous regime, we will show that in fact unidirectional pinning can be observed in the Shifox model. Furthermore, we will show that it can be observed by changing both the scaling parameter $\tau$, as well as the more experimentally friendly pacing period BCL. In the next section, we study the spatial wavelength of solutions, compare the scaling properties in the smooth regime and the discontinuous regime. In particular, we show that, in agreement with our predictions, the wavelength scales sub-linearly in the smooth regime, but linearly in the discontinuous regime. Finally, in the last section we study the jumping points of solutions. In addition to showing the symmetrizing effect that changes of parameters have on the shape of profiles about each node, we
use our reduced model to predict jumping points of normal jumps.

6.1 Computing $\Lambda$ from CV Restitution Curves

We show here that the CV restitution length scale $\Lambda$ that is so important in the dynamics of the reduced model can be computed from the numerically computed restitution curves of ionic models. Recall that the CV restitution curve describes the velocity with which a stimulus propagates as a function of the DI. Example CV restitution curves were illustrated in Chapter 2 in Figures 2.10 and 2.11. Also, recall from the derivation in Chapter 3 that the CV restitution length scale $\Lambda$ is given by

$$\Lambda = \frac{CV^2(D^*)}{2CV'(D^*)},$$

(6.1)

where $D^*$ is the critical DI at the onset of alternans in a cable of tissue. In Figure 6.1 we plot shorter portions of $CV(DI)$ and $CV^2(DI)/2CV'(DI)$ as computed numerically for the Shifox model for several values of $\tau$.

![Figure 6.1: A portion of several CV and CV$^2$/2CV' curves for the Shifox model for several different values of the scaling parameter $\tau$.](image)

We now make a few remarks of the data plotted in Figure 6.1. First, despite the restitution curves being so smooth, due to their flatness any noise becomes greatly amplified in the quantity $CV^2/2CV'$, so one should use a higher-order finite difference method for computing the derivative.
Next, we argued in Chapter 3 that because increasing the scaling parameter $\tau$ causes the CV restitution curve to unflatten, due to the fact that $\Lambda \sim 1/CV'(D^*)$ this effectively decreases $\Lambda$. We remind the reader that the scaling parameter $\tau$ scales the timescale of the sodium $j$-gate dynamics, changing the propagation of stimuli along the cable. In Figure 6.1 we see that as $\tau$ increases, the entire curve $CV^2(DI)/2CV'(DI)$ is shifted down, confirming our hypothesis. Finally, to actually calculate $\Lambda$ we need to evaluate $CV^2(DI)/2CV'(DI)$ at the critical DI where the onset of alternans occurs in a cable of tissue. We find that for a wide range of $\tau$ this critical value is $D^* \approx 237.5$ ms, which we denote with a black vertical dot-dashed line in Figure 6.1. In Figure 6.2 we plot the $\Lambda$ values computed for the Shifox model over a range of $\tau$ values.

![Figure 6.2: CV restitution length scale $\Lambda$ computed from the Shifox model for several values of the scaling parameter $\tau$.](image)

**6.2 Unidirectional Pinning**

We now show that the phenomenon of unidirectional pinning can be observed in the Shifox model. Recall from Chapter 5 that we observed this phenomenon by first decreasing $r$ or $\Lambda$ to move the nodes towards the pacing site at $x = 0$, then restoring the parameters to their original values, noting that the nodes stayed pinned in their locations close to the pacing site. Furthermore, from the numerical investigation above, we know that by increasing the scaling parameter $\tau$ we can effectively decrease $\Lambda$, while decreasing $\tau$ effectively increases $\Lambda$. We note that since we are
interested in qualitatively confirming the phenomenon of unidirectional pinning, we will not present
the explicitly computed Λ values at this point.

Thus, we begin by presenting an experiment where we use τ to induce unidirectional pinning. We begin by obtaining a steady-state discontinuous pattern at $BCL = 330$ ms with $τ = 9.0$. Next, we slowly increase $τ$ to 9.8 and then slowly restore it to 9.0. In Figure 6.3 we present results from this experiment. In the first panel we plot $c_n(x)$ profiles at $τ = 9.0$, 9.4, and 9.8 in red, green, and blue, respectively, as we first increase $τ$. We note that as $τ$ increases, the location of all nodes move in towards the pacing site at $x = 0$. In the second panel we plot $c_n(x)$ profiles at $τ = 9.8$, 9.4, and 9.0 in blue, green, and red, respectively as we decrease $τ$, restoring it back to its original value. As expected, we see that the nodes remain pinned in their locations closer towards the pacing site, thus confirming that unidirectional pinning can be observed in detailed ionic models, and is not simply an artifact of the reduced system studied previously. We hypothesize here that unidirectional pinning can be observed in any ionic model that is detailed enough to robustly capture the calcium-cycling dynamics and induce calcium-driven alternans.

Figure 6.3: Illustration of unidirectional pinning in the Shifox model via changing CV restitution. Amplitude of calcium alternans $c(x)$ as $τ$ is slowly increased from 9.0 to 9.8 (left panel) then slowly decreased from 9.8 to 9.0 (right panel).

Despite the fact that this experiment confirms that unidirectional pinning can be observed in detailed ionic models, these results may be difficult to replicate in real cardiac tissue, i.e., in laboratory experiments. This is because there is likely not a way to effectively change the
scaling parameter $\tau$ quickly “at will” in both direction. On the other hand, possibly the easiest parameter in the Shifox model to change in the laboratory is the BCL. Thus, we now present and experiment where we can observe unidirectional pinning by only changing the BCL in order to motivate laboratory experiments.

We first note that in the reduced model, decreasing and increasing the degree of calcium instability $r$ has the same hysteretic effect on node dynamics as decreasing and increasing $\Lambda$. Furthermore, when the BCL is decreased in an ionic model, this causes an effective increase in the degree of calcium instability due to the fact that it gives the calcium dynamics less time to equilibrate between beats. Thus, to decrease and increase $r$, we can increase and decrease the BCL, respectively. We now present an experiment where, after obtaining a steady-state discontinuous solution at 330 ms with $\tau = 9.0$, we first slowly increase the BCL to 334 ms, then slowly restore it to 330 ms. In Figure 6.4 we present our results. In the first panel we plot $c_n(x)$ at BCL= 330, 332, and 334 ms in red, green and blue, respectively, as we increase BCL. We note that each node moves in towards the pacing site at $x = 0$. In the second panel we plot $c_n(x)$ at 334, 332, and 330 ms in blue, green, and red, respectively, as we decrease BCL to restore it to its original value. Again, we see that the nodes remain pinned in the locations closer to the pacing site.

Figure 6.4: Illustration of unidirectional pinning in the Shifox model via changing BCL. Amplitude of calcium alternans $c(x)$ as BCL is slowly increased from 330 ms to 334 ms (left panel) then slowly decreased from 334 ms to 330 ms (right panel).
6.3 Scaling of Spatial Wavelengths

We now move to study the scaling of spatial wavelengths of solutions in ionic models. Recall that in Chapter 4 we studied the scaling of the spatial wavelength $\lambda_s$ for solutions of the reduced model in the smooth regime. In particular, we found that $\lambda_s \sim \Lambda^{1/3}$ or $\Lambda^{1/2}$, depending on whether solutions had a finite or zero velocity. We note here that these wavelengths were valid near onset, but we hypothesize that the spatial wavelength of smooth solution further away from onset still scale sub-linearly with $\Lambda$. On the other hand, we found in Chapter 5 that the spatial wavelength for solutions of the reduced model in the discontinuous regime scales like $\lambda_s \sim \Lambda$.

We now study the scaling of $\lambda_s$, defined as twice the distance between adjacent nodes, in the Shifox model. We begin by obtaining steady-state smooth and discontinuous patterns by choosing BCL= 345 ms and 330 ms, respectively, with a scaling parameter $\tau = 10$, then slowly decreasing $\tau$ and tracking the evolution of $\lambda_s$. Thus, we can plot the resulting wavelength $\lambda_s$ vs the CV restitution length scale $\Lambda$, which we computed above. In Figure 6.5 we plot the results for the smooth (BCL= 345 ms) and discontinuous (BCL= 330 ms) cases in blue circles and red crosses, respectively. We note that the range of $\Lambda$ values that we have calculated is not large enough to plot our data in log-log scale to attempt to fit the data, but it is clear from the concavity we see that in the smooth case $\lambda_s$ scales sub-linearly with $\Lambda$ while in the discontinuous case $\lambda_s$ appears to scale linearly with $\Lambda$.

6.4 Jumping points in Discontinuous Solutions

We conclude this Chapter by studying the jumping points of discontinuous solutions in ionic models. We first consider the the symmetrizing effect we observed in the reduced model, where by increasing $r$ or $\Lambda$ once a steady-state discontinuous pattern has formed, we found that the asymmetry decreased. Here we test this with the Shifox model by first obtaining a steady-state discontinuous solution, then decreasing the scaling parameter $\tau$, which we have seen above effectively increases the CV restitution length scale $\Lambda$, and measuring the quantity $\Delta = (|c_+| - |c_-|)/(|c_{+,0}| - |c_{-,0}|)$. 

In Figure 6.6 we plot the results from using BCL= 330 ms, and decreasing $\tau$ from 10 to 8. Rather than plotting $\Delta$ vs $\tau$, to make more explicit the connection with the reduced model, we plot $\Delta$ vs $\Lambda$.

Initially, we see in Figure 6.6 that the asymmetry $\Delta$ decreases from 1 as expected. We also note that $\Delta$ becomes negative at $\Lambda \approx 58$, indicating that the length scale of asymmetry $w$ in the Green’s function is non-zero, as we noted in Chapter 5. To illustrate this, we plot in Figure 6.7 the profiles $c(x)$ taken from our experiment at $\Lambda = 41.76, 52.68, 71.74$, plotted in blue, red and green, respectively. As we increase $\Lambda$ we see that the shape of profiles about the nodes transition from $|c_-| < |c_+|$ ($\Lambda = 41.76$) to $|c_-| > |c_+|$ ($\Lambda = 71.74$). In Chapter 7 we will show how the symmetry-breaking of non-zero $w$ yields this phenomenon.

We now turn to study the jumping values of normal jumps, i.e., when a steady-state discontinuous pattern first forms. In particular, we found in the reduced model that for a normal jump, the jumping points only depended on the terms describing the local calcium dynamics in Equation (3.22). Recall that in the absence of the effect of voltage, we have that these local dynamics are given by

$$c_{n+1}(x) = -rc_n(x) + f[c_n(x)]$$

$$= -rc_n(x) + gc_n^3(c) + \chi_1 c_n^5(x) + \cdots + \chi_m c_n^{2m+3}(n).$$

(6.3)
Figure 6.6: Asymmetry $\Delta$ in the Shifox model vs $\Lambda$ as the scaling parameter $\tau$ is decreased from 10 to 8.

For the sake of developing theory we have focused the majority of this Thesis on the simple cubic case where $g = 1$ and $\chi_1, \ldots, \chi_m = 0$. However, in Chapter 5 we generalized our theory for normal jumping points to more general nonlinearities in Equation (6.3). We note here that for the case of a general cubic, i.e., $g \neq 0$, $\chi_1, \ldots, \chi_m = 0$, we obtain jumping points

$$c_- = \pm \sqrt{(r-1)/3g}, \quad c_+ = \mp 2\sqrt{(r-1)/3g}, \quad (6.4)$$

where we note that $|c_+| = 2|c_-|$. For a general quintic, i.e., $g, \chi_1 \neq 0$, $\chi_2, \ldots, \chi_m = 0$, we showed that the jumping points were given by

$$c_- = \pm \sqrt{-3g + \sqrt{9g^2 + 20\chi_1(r-1)}} / 10\chi_1, \quad c_+ = \mp \sqrt{-g + \sqrt{g^2 + 4\chi_1(r-1)}} / 2\chi_1. \quad (6.5)$$

For more general nonlinearities $c_-$ and $c_+$ can be found by solving

$$f'(c_-) = r - 1, \quad (r-1)c_+ - f(c_+) = A(x_0), \quad (6.6)$$

where $A(x_0) = (r-1)c_- - f(c_-)$.

We now use this theory to predict the value of jumping points for normal jumps in the Shifox model. In order to do this, we need to first estimate the degree of calcium instability $r$, and second estimate the function $f(c)$, i.e., estimate the coefficients $g$ and $\chi_1, \ldots, \chi_m$ from the ionic model. For the case of a cubic nonlinearity, this turns out to be very simple. Given a steady-state value of
Figure 6.7: Calcium profiles \( c(x) \) plotted for increasing \( \Lambda \) values 41.76, 52.68, and 71.74 in blue, red, and green, respectively.

\[
c_\infty = c_n = -c_{n+1}, \text{ we have that } \]
\[
(r - 1)c_\infty = gc_\infty^3, \tag{6.7}
\]

which can be rearranged and inserted into Equations 6.4 to obtain

\[
c_- = \pm c_\infty/\sqrt{3}, \quad c_+ = \mp 2c_\infty/\sqrt{3}. \tag{6.8}
\]

However, for quintic nonlinearities and beyond, the estimations become more difficult.

We begin by noting that for a single cell, since \( c_{n+1} = -rc_n + c_n^3 \), the degree of instability \( r \) can be estimated by observing the transient dynamics of \( c_n \) perturbed off of the unstable period-one orbit \( c_{n+1} = c_n = 0 \). Immediately after the perturbation we have that \( c_n \ll 1 \), so we can neglect the cubic term and estimate

\[
r \approx -\frac{c_{n+1}}{c_n}. \tag{6.9}
\]

This can be done numerically by pacing a single cell with both a voltage clamp and a calcium clamp, then turning off the calcium clamp and observing the trajectory of \( c_n \). In Figure 6.8 we plot the results from estimating \( r \) over a large range of BCL for the Shifox model. Of course, this method is only valid if \( r > 1 \), i.e., if alternans form and the period-one solution is in fact unstable.

Next, to estimate the nonlinearity \( f(c) \) we need several measurements of \( r \), obtained by the method described above, and corresponding steady-state values \( c_\infty \). We note that \( f(c) \) should
satisfy

\[ r - 1 = \frac{f(c_\infty)}{c_\infty}, \]  

(6.10)

so for a given form of \( f(c) \) with \( g, \chi_1, \ldots, \chi_m \neq 0 \), these coefficients can be found by applying a least-squares fit to Equation (6.10), provided we have at least \( m + 1 \) measurements of \( r \) and \( c_\infty \).

In Figure 6.9 we plot the results from finding the best quintic fit of \( f(c) \), plotted in dashed red, to \( c_\infty \) data, plotted in blue dots, using the \( r \) values calculated above.

Given estimates of the degree of instability \( r \) and the nonlinearity \( f(c) \), we can now predict the normal jumping points \( c_- \) and \( c_+ \) with Equations (6.4), (6.5), or (6.6). In Table 6.1 we present the actual \( c_- \) and \( c_+ \) values as observed from simulation, and several predictions using estimated cubic, quintic, and seventh-order nonlinearities. Results vary slightly depending on the assumed form of \( f(c) \), however, each method gives a reasonable prediction of the observed jumping values.

<table>
<thead>
<tr>
<th>jumping points</th>
<th>simulation</th>
<th>cubic</th>
<th>quintic</th>
<th>seventh-order</th>
</tr>
</thead>
<tbody>
<tr>
<td>( c_- )</td>
<td>0.2307</td>
<td>0.256014</td>
<td>0.31257</td>
<td>0.300979</td>
</tr>
<tr>
<td>( c_+ )</td>
<td>0.3636</td>
<td>0.512028</td>
<td>0.508705</td>
<td>0.509877</td>
</tr>
</tbody>
</table>

Table 6.1: Simulation and prediction of jumping points in the Shifox model.
Figure 6.9: The quintic fit of $f$ (dashed red) to $c_\infty$ data (blue dots) from the Shifox model.
Chapter 7

Comment on Inferring the Origin of Alternans

Thus far we have developed a rich understanding of the generic spatiotemporal dynamics of calcium-driven alternans in a cable of tissue using both analytical and numerical methods. Furthermore, we have also commented on the similarities and dissimilarities of these dynamics to those seen when alternans are voltage-driven. One major question in the research of cardiac dynamics that persists is how to identify the origin of alternans. That is to say, if we observe alternans (numerically or experimentally), how can we identify them as calcium-driven or voltage-driven?

Using the detailed Shifox model with the standard cable equation (i.e., the same detailed ionic model we used in this Thesis) this question is investigated in Reference [52]. The results of this study show that when spatially discordant alternans are present, then the length scale of the phase reversal depends on whether alternans are voltage- or calcium-driven. In particular, they find that this length scale is, relatively speaking, large for voltage-driven alternans and small for calcium-driven alternans. This is equivalent to saying that the slope of the alternans amplitude profile near a phase-reversal is mild for voltage-driven alternans and steep for calcium-driven alternans. These results suggest that we can identify alternans as voltage- or calcium-driven simply by inspecting the length scale of phase reversals in spatially discordant patterns.

Our results shed more light on this issue. References [14, 16] show that voltage-driven alternans only form smooth wave profiles with relatively mild phase reversals. Furthermore, we have shown using both detailed ionic models as well as an analytically-tractable reduced model
that phase reversals can be very steep (given by discontinuous jumps) for calcium-driven alternans with large degrees of instability. However, we have also shown that there is a smooth regime for calcium-driven alternans with milder degrees of instability.

This suggests that if the length scale of phase-reversals in discordant patterns is very short, then we can indeed conclude that alternans are calcium-driven. However, if these phase-reversals are relatively thick, then alternans can be either voltage-driven or calcium-driven. In the first section we will introduce a special case of the reduced system given by Equations (3.22) and (3.23) where we assume a flat CV restitution curve. In the second section we will perform a bifurcation analysis on this special reduced system. In the third section we will quantify the length scale of phase reversals of calcium-driven alternans and connect our results to the discussion above. Finally, in the last section we will study in detail the the jumping points of \( c(x) \) in the flat CV case when the Green’s function has a non-zero asymmetry length scale \( w \) and connect these results to finding presented in Chapter 6.

### 7.1 Alternans with Flat CV Restitution

We now consider the system given by Equations (3.22) and (3.23) in the limit of flat CV restitution corresponding to the portion of the curve in Figure 2.10 for large DI. Recalling that the CV parameter \( \Lambda \) is inversely proportional to the slope of the CV restitution curve, we have that in the limit of flat CV restitution \( i.e., CV'(DI) \to 0 \) \( \Lambda^{-1} \to 0 \), in which case two of the integral terms in Equations (3.22) and (3.23) vanish and we obtain the simplified system

\[
c_{n+1}(x) = -rc_n(x) + c_n^3(x) - \alpha a_n(x), \quad (7.1)
\]

\[
a_{n+1}(x) = \int_0^L G(x' - x)[-\beta a_n(x') + \gamma c_{n+1}(x')]dx'. \quad (7.2)
\]

We note that this system would also model the dynamics in a cable of tissue where each cell is paced simultaneously.

Without any CV restitution, the system given by Equations (7.1) and (7.2) no longer has any mechanism to spontaneously form discordant alternans aside from aggregation of initial condition.
When discordant alternans do form from initial conditions, we find the same solution regimes that appear from the system with CV; namely regimes with no alternans, smooth patterns, and discontinuous patterns. In Figure 7.1 we present an example of smooth steady-state $c_n(x)$ and $a_n(x)$. Parameters used are $r = 0.9$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$. For initial conditions we use random noise where the value $c_0(x)$ and $a_0(x)$ at each point is drawn from the uniform distribution $U[-\epsilon, \epsilon]$ with $\epsilon = 0.02$. We note that, due to the initial condition, spatially discordant regions form irregularly along the cable in patterns with no set wavelength while both $c_n(x)$ and $a_n(x)$ remain smooth.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7_1.png}
\caption{For flat CV: A smooth alternans solution $c(x)$ and $a(x)$ of Equations (7.1) and (7.2) for $r = 0.9$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.}
\end{figure}

In Figure 7.2 we present an example of discontinuous steady-state solutions $c(x)$ and $a(x)$. Parameters used are $r = 1.2$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$. Again, initial values of $c_0(x)$ and $a_0(x)$ at each point are drawn from the uniform distribution $U[-\epsilon, \epsilon]$, and again spatially discordant regions form irregularly along the cable in patterns with no set wavelength. Furthermore, $c_n(x)$ develops discontinuities at the nodes while $a_n(x)$ remains smooth.

Because the presence and location of phase reversals in solutions is at the mercy of initial conditions, we will study properties of solutions where a single phase reversal exists at the center of a cable that extends from $x = -L/2$ to $x = L/2$. This can be done by setting the initial conditions to $c_0(x) = \epsilon$ for $x <= 0$ and $c_0(x) = -\epsilon$ for $x > 0$ and similarly for $a_0(x)$. In Figure 7.3 we show a
Figure 7.2: For flat CV: A discontinuous alternans solution $c(x)$ and $a(x)$ of Equations (7.1) and (7.2) for $r = 1.2$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.

Phase reversal located at the center of a cable for several $r$ values ranging from 0.7 to 1.3. Other parameters are $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$. Profiles are colored so that solutions for $r = 0.7$ are blue and solutions for $r = 1.3$ are red, and other colors interpolate in between. As $r$ increases from 0.7 solutions form smooth profiles shaped approximately like hyperbolic tangents while the slope at the node $x = 0$ becomes steeper. However, at some intermediate $r$ value these profiles develop a jump discontinuity at the node while the amplitude of $c_n(x)$ increases. This discontinuity becomes very evident for large $r$ values, e.g. near 1.3.

Similar to Equations (3.22) and (3.23) that incorporate CV, the solutions to Equations (7.1) and (7.2) have three regimes of solutions: no alternans, smooth profiles, and discontinuous profiles. Furthermore, there are two bifurcations $r_1^{\infty}$ and $r_2^{\infty}$ that are analogous to those for finite CV. We now turn to study these bifurcations as well as phase reversals in these profiles.

### 7.2 Bifurcation Analysis

To classify the different regimes of solutions and the bifurcations between them, we will consider a cable extending from $x = -L/2$ to $x = L/2$ in the limit of $L \to \infty$ and assume a single node exists at $x = 0$. Furthermore, we will consider the case of a symmetric Green’s function, i.e., a zero asymmetry length scale parameter $w$. In this scenario the steady-state solutions $c(x) = \cdots$.
Figure 7.3: Shape of phase reversals in solutions $c(x)$ of Equations (7.1) and (7.2) with flat CV for several $r$ values ranging from 0.7 to 1.3. Other parameters are $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.

c_n(x) = -c_{n+1}(x)$ and $a(x) = a_n(x) = -a_{n+1}(x)$ are anti-symmetric, i.e., satisfy $c(-x) = -c(x)$ and $a(-x) = -a(x)$, which is true for any symmetric Green’s function $G$ (even if it is chosen to be non-Gaussian). This can be observed in Figure 7.3 and verified in Equations (7.1) and (7.2).

Furthermore, we define the quantities $c_0 = \lim_{x \to 0^+} c_n(x)$ and $c_\infty = \lim_{x \to \infty} c(x)$ that describe the value of $c(x)$ very near and very far, respectively, from the node.

We begin our analysis by inserting Equation (7.2) into Equation (7.1) ad infinitum, which yields an equation containing an infinite sum of multiple integrals and products of Green’s functions:

$$c_{n+1}(x) = -rc_n(x) + c_n^3(x) - \eta \sum_{m=0}^{\infty} \beta^m \prod_{j=1}^{m+1} G(x_j - x_{j-1}) \int c_{-m}(x_{m+1}) dx_{m+1} \cdots dx_1. \quad (7.3)$$

Since $w = 0$, $G$ is Gaussian with standard deviation $\xi$, so we can rearrange the order of integration and, using that the convolution of two Gaussians is another Gaussian whose standard deviation is the sum of the two previous standard deviations, obtain

$$c_{n+1}(x) = -rc_n(x) + c_n^3(x) - \eta \sum_{m=0}^{\infty} (-\beta)^m \int G_{(m+1)\xi^2}(x' - x) c_{-m}(x') dx' \quad (7.4)$$

$$= -rc_n(x) + c_n^3(x) - \eta \int \widehat{G}_{\xi^2}(x' - x) c_n(x') dx', \quad (7.5)$$
where we have assumed period-two solutions \( c_{n+1}(x) = -c_n(x) \), \( G_{\xi^2} \) denotes a Gaussian with variance \( \xi^2 \), and \( \tilde{G}^2_{\xi}(x' - x) = \sum_{m=0}^{\infty} \beta^m G_{(m+1)\xi^2}(x' - x) \). Next, we use the fact that \( c(x) \) is odd and has only one node at \( x = 0 \) to find that

\[
\lim_{x \to 0^+} \int \tilde{G}^2_{\xi}(x' - x)c(x')dx' = 0, \tag{7.6}
\]

\[
\lim_{x \to \infty} \int \tilde{G}^2_{\xi}(x' - x)c(x')dx' = \lim_{x \to \infty} \frac{c(x)}{1 - \beta} = \frac{c_\infty}{1 - \beta}. \tag{7.7}
\]

Finally, we take the limits as \( x \to 0^+ \) and \( x \to \infty \), respectively, of Equation (7.5), which yields

\[
c_\infty = \begin{cases} 
0 & \text{if } r \leq 1 - \frac{\eta}{1 - \beta}, \\
\pm \sqrt{r - 1 + \frac{\eta}{1 - \beta}} & \text{if } r > 1 - \frac{\eta}{1 - \beta},
\end{cases} \tag{7.8}
\]

\[
c_0 = \begin{cases} 
0 & \text{if } r \leq 1, \\
\pm \sqrt{r - 1} & \text{if } r > 1.
\end{cases} \tag{7.9}
\]

To verify these results we compute \( c_\infty \) and \( c_0 \) from direct numerical simulations of Equations (7.1) and (7.2) and compare with our theoretical predictions given by Equations (7.8) and (7.9). In Figure 7.4 we plot results from simulations (connected blue circles) and our theoretical predictions (dashed red curve), noting that results agree extremely well. Other parameters are \( \alpha, \gamma = \sqrt{0.3}, \beta = 0.1, \xi = 1, \) and \( w = 0. \)

Using this analysis, we can classify the bifurcations between regimes as follows. The transition from no alternans to smooth profiles occurs at \( r = r_1^\infty \equiv 1 - \frac{\eta}{1 - \beta} \). This corresponds to the profiles \( c_n(x) \) and \( a_n(x) \) taking on non-zero values except at the node, but remaining smooth. The transition from smooth profiles to discontinuous profiles then occurs at \( r = r_2^\infty \equiv 1 \). This corresponds to the profile \( c_n(x) \) developing a jump-discontinuity at precisely \( x = 0 \).

### 7.3 Length Scale of Phase-Reversals

We now seek to quantify the length scale of phase reversals of steady-state solutions \( c_n(x) \) of Equations (7.1) and (7.2). Since steady-state solutions have minimum and maximum values of \( \pm c_\infty \) and a node at \( x = 0 \), we define the length scale of a phase reversal as \( l = 2c_\infty / c'(0) \). We begin
by assuming a period-two solution of the form \(-c_{n+1}(x) = c_n(x) = c(x)\) in the smooth regime and take a derivative with respect to \(x\) of Equation (7.5) and obtain

\[
(r - 1)c'(x) = 3c^2(x)c'(x) - \eta \int \partial_x \hat{G}_\xi^2(x' - x)c(x')dx'.
\]  

(7.10)

Next, we use that \(\partial_x \hat{G}_\xi^2(x' - x) = -\partial_{x'} \hat{G}_\xi^2(x' - x)\), integrate by parts, and evaluate at \(x = 0\) to obtain

\[
c'(0) = \frac{\eta}{1 - r} \int \hat{G}_\xi^2(x')c'(x')dx'.
\]  

(7.11)

Finally, we expand each Gaussian \(G_{(m+1)\xi}^2(x') = 1/\sqrt{2\pi(m+1)\xi^2} + O(x'^2)\) and integrate to obtain

\[
c'(0) = \frac{2\eta c_\infty}{(1 - r)\beta \sqrt{2\pi \xi^2}} Li_{1/2}(\beta),
\]  

(7.12)

where we have used the polylogarithm function \(Li_s(z) = \sum_{j=1}^{\infty} z^j / j^s\). We note that the approximation \(G_{(m+1)\xi}^2(x') = \text{constant}\) is valid for profiles with thin phase-reversals, i.e., smooth solutions with \(r\) near \(r^\infty_2\). Given this form of \(c'(0)\), the length scale \(l\) is simply given by

\[
l = \frac{(1 - r)\beta \sqrt{2\pi \xi^2}}{\eta Li_{1/2}(\beta)}.
\]  

(7.13)
One main result is that as $r \to r_2^\infty$ we find that the values $c'(0)$ and $l$ tend to infinity and zero, respectively, which agrees with our theory from the previous section that a discontinuity develops at $r = r_2^\infty = 1$. We note that since we assumed a smooth profile, Equation (7.13) holds for $r \leq 1$, while $l = 0$ for $r > 1$ where $c(x)$ is not differentiable at the node.

![Figure 7.5](image.png)

Figure 7.5: For several different discretization refinements $\Delta x$ ranging from 0.1 (blue) to 0.001 (red), the value of $c'(0)$ as calculated from direct simulation of Equations (7.1) and (7.2) vs theoretical predictions given by Equation (7.12), plotted in dashed black. Other parameters are $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0.2$, $\xi = 1$, and $w = 0$.

We first verify that our theory for the value of $c'(0)$ holds by computing $c'(0)$ directly from numerical simulations of Equations (7.1) and (7.2) over a range of $r$ values with different discretization refinements $\Delta x$ and comparing to the theoretical prediction given by Equation (7.12). In Figure 7.5 we plot results from simulations with $\Delta x$ ranging from 0.1 (blue) to 0.001 (red) and our theoretical prediction in dashed black. We note that as $\Delta x$ decreases the numerically computed $c'(0)$ converges towards our prediction, as expected.

Finally we verify that our theory for the length scale $l$ holds by computing $l$ directly from numerical simulations of Equations (7.1) and (7.2) for several $r$ values and comparing to the theoretical prediction given by Equation (7.13). In Figure 7.6 we plot results from simulations with $\Delta x = 0.001$ (connected blue circles) and our theoretical prediction (dashed red). We note that our theoretical prediction holds very well, both below $r = 1$ and above $r = 1$, where the length scale vanishes.
7.4 Jumping Points for an Asymmetric Green’s Function

We close this chapter by studying the jumping points of the calcium profile \( c(x) \) in the limit of flat CV restitution when the asymmetry length scale \( w \) of the Green’s function, given by Equation (3.6), is non-zero. In the bifurcation analysis above, we found that when \( w = 0 \) the jumping points of the node located at \( x = 0 \) are \( |c_-|, |c_+| = |c_0| = \sqrt{r-1} \). This followed directly from the fact that for anti-symmetric steady-state solutions \( c(x) = c_n(x) = -c_{n+1}(x) \), \( c(-x) = -c(x) \), the integral term in Equation (7.5) vanished due to the symmetry of \( G \). We note that these jumping points correspond to those we found in the \( \Lambda \to \infty \) limit in Chapter 5, i.e., the dashed black line in Figure 5.3. However, as we noted in Chapters 5 and 6, when \( w \neq 0 \) this symmetry is broken, yielding jumping point values \( |c_-| \neq |c_+| \). Here we provide an analysis describing this behavior.

We begin by defining the symmetric and antisymmetric parts, \( G_s \) and \( G_a \), of the Green’s function \( G \), given by

\[
G_s(x) = \frac{G(x) + G(-x)}{2}, \tag{7.14}
\]

\[
G_a(x) = \frac{G(x) - G(-x)}{2}. \tag{7.15}
\]
We note that $G(x) = G_s(x) + G_a(x)$, and for the case of $w = 0$ we have that $G_s = G$ and $G_a$ is identically zero. To illustrate the shape of asymmetric Green’s functions, we plot in Figure 7.7 the Green’s function $G$ in blue, as well as its antisymmetric and symmetric parts $G_a$ and $G_s$, in red and green, respectively, using $\xi = 1$ and $w = 0.6$. The symmetric part $G_s$ is given by a Gaussian, while the effect of $G_a$ is to add and subtract mass from $G$ for small $x$ greater than and less than zero, respectively, and to subtract and add mass to $G$ for large $x$ greater than and less than zero, respectively.

![Figure 7.7](image.png)

Figure 7.7: The green’s function $G$ [Equation (3.6)] for width and asymmetry length scales $\xi = 1$ and $w = 0.6$ (blue curve), along with its antisymmetric and symmetric parts $G_a$ and $G_s$ [Equations (7.14) and (7.15)] plotted in red and green, respectively.

To proceed with our analysis, we consider for simplicity the case of zero APD restitution, i.e., $\beta = 0$, and we choose the steady-state solutions $c(x) = c_n(x) = -c_{n+1}(x)$ to be positive for $x > 0$ and negative for $x < 0$, similar to those plotted in Figure 7.3. Thus, we have that in the discontinuous regime $c_- < 0$ and $c_+ > 0$. Furthermore, we note that the antisymmetric solution for $w = 0$ is monotonically increasing with $|c(x)| > |c(y)|$ for $|x| > |y|$. From Equation (7.5), $c(x)$ must satisfy

$$c^3(x) - (r - 1)c(x) - \eta \int G(x' - x)c(x')dx' = 0.$$  \hspace{1cm} (7.16)

However, for $w \neq 0$, the antisymmetric solution $c(x) = -c(-x)$ described above is no longer a solution of Equation (7.16). This follows from the fact that for $x > 0$ the mass of the positive
and negative parts of \( G_a(x) \) (which has zeros at \( x = 0, \pm \sqrt{2}\xi \)) cancel out exactly. Similarly, the mass of the positive and negative parts of \( G_a(x) \) for \( x < 0 \) cancel out. Thus, for a monotonically increasing \( c(x) \), the integral term in Equation 7.16 is no longer zero, and in fact it is negative. Thus, a steady-state solution \( c(x) \) of Equation (7.16) can no longer satisfy \( c(x) = -c(-x) \), and in fact we will see that the jumping point \( c_- \) and \( c_+ \) can no longer satisfy \(|c_-| = |c_+|\).

We can predict which direction the jumping points move in by considering the quantity

\[ \Delta c_n(x) = (-c_{n+1}(x)) - c_n(x) \text{ near } x = 0. \]

We note that \( \Delta c_n(x) \) gives the evolution of \( c_n(x) \) from beat \( n \) to \( n+1 \) after accounting for a flip in sign. Using Equation (7.5) and considering the limit \( x \to 0^+ \), we find that

\[ \Delta c_n^+ = (r - 1)c_n^+ - c_n^{+3} + \eta \int G(x')c(x')dx'. \]

(7.17)

Since the integral in Equation (7.17) is a non-local term that depends on all of \( c(x) \), we cannot find the exact steady-state value of \( c_+ \), for which \( \Delta c_n^+ = 0 \). However, since the integral term yields negative values for antisymmetric \( c(x) = -c(-x) \) we can conclude that from an initial guess of \( c_0^+ = \sqrt{r-1} \) and antisymmetric solutions \( c(x) \) found in the \( w = 0 \) case, the difference \( \Delta c_n^+ < 0 \) and \( c_n^+ \) will decrease, yielding a steady-state value of \( c_+ < \sqrt{r-1} \). By a similar argument, we find that the steady-state value of \( c_- < -\sqrt{r-1} \). Thus, we can conclude that for \( w \neq 0 \) the steady-state profile \( c(x) \) is no longer antisymmetric, and has as jumping points that satisfy \(|c_-| > |c_+|\).

To illustrate this behavior, in Figure 7.8 we plot an example steady-state solution \( c(x) \) of Equation (7.1) and (7.2) using an asymmetric Green’s function in blue. Other parameters are \( r = 1.15, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \) and \( w = 1 \) We also plot the antisymmetric and symmetric parts of \( c(x) \), defined as \( c_a(s) = [c(x) - c(-x)]/2 \) and \( c_s(x) = [c(x) + c(-x)]/2 \), in red and green, respectively. We note that the steady-state solution \( c(x) \) is a small departure from its anti-symmetric part \( c_a(x) \), characterized by its symmetric part \( c_s(x) \), which is negative, causing an overall negative shift. Thus, we see that in absolute value the right jumping point \( c_- \) is larger than the left jumping point \( c_+ \), as our analysis predicts. Finally, we note that this phenomenon explains the results of the ionic model simulations presented in Figures 6.6 and 6.7, where the measure of asymmetry \( \Delta \) becomes
negative, indicating that $|c_-| > |c_+|$. 

Figure 7.8: The shape of an example solution $c(x)$ of Equations (7.1) and (7.2) with flat CV and an asymmetric Green’s function. We plot the solution $c(x)$ in blue along with its antisymmetric and symmetric parts $c_a(x)$ and $c_s(x)$ in red and green, respectively. Other parameters are $r = 1.15$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 1$. 
Chapter 8

Discussion and Conclusions

We now conclude this Thesis with a brief discussion of our results. First, we consider the physiological implications of our results. Here we will discuss generic physiological properties of calcium-driven alternans in tissue and compare and contrast calcium-driven alternans with voltage-driven alternans. Second, we discuss the possibility of laboratory experiments inspired by our results. Finally, we suggest a few directions that future research may take and extensions to existing work describing the analytical treatment of cardiac alternans.

8.1 Physiological Implications

In this Thesis we have presented many results describing the spatiotemporal dynamics of calcium-driven alternans in tissue. These results have been obtained from our reduced model given by Equations (3.22) and (3.23) by means of both analytical and numerical techniques. Furthermore, many of these results have been observed and describe the dynamics in detailed ionic models, both qualitatively and quantitatively, confirming that they are not simply artifacts of our reduced model.

We have found that when alternans are driven by a calcium-mediated instability, there are three regimes of different dynamics. As the degree of instability increases, these regimes are: (i) no alternans, (ii) smooth wave patterns, and (iii) discontinuous patterns. The characteristic that makes calcium-driven alternans novel is the existence of the discontinuous regime. In terms of the reduced model, the development of the discontinuity in calcium profiles follows from the fact that the right-hand-side of Equation (3.22) is not smoothed by a Green’s function and therefore has no
smoothness constraint. Physiologically, this is a reflection of the fact that calcium concentrations $[\text{Ca}^{2+}]_i$ diffuse across tissue on a timescale that is much slower than the timescales of voltage diffusion as well as the dynamics of all ion currents.

Importantly, we can now compare the dynamics of calcium-driven alternans to voltage-driven alternans. On one hand, when the degree of calcium instability is relatively mild, we find that the dynamics of the two cases are analogous. In fact, the predicted onset values, velocities, and spatial wavelengths are equivalent. Since the dynamics of nodes in spatially discordant alternans are particularly important to understand, we highlight here that the spatial wavelength is particularly important, since it predicts the spacing of the nodes that form, i.e., nodes form at every half wavelength. On the other hand, when alternans are voltage-driven there are no dynamics that correspond to the discontinuous regime of solutions in calcium-driven alternans, corresponding to larger degrees of calcium instability. In fact, discontinuous solutions in the voltage-driven case are non-physical due to the diffusion of voltage across tissue. Additionally, we note that the spatial wavelength of solutions in this regime scales linearly with the CV restitution length scale, as opposed to the sub-linear scaling relations we have found in the smooth regime. Thus, the spacing of nodes for calcium-driven alternans at relatively large degrees of calcium instability.

The most novel property of calcium-driven alternans that we have uncovered is undoubtedly the presence of hysteresis in the discontinuous regime. Through various simulations we have shown that once a steady-state discontinuous profile has formed, changes of parameters can cause (i) the shape of profiles to symmetrize about each node and (ii) node locations to move towards the pacing site without any hope of moving away from the pacing site. We call this latter property unidirectional pinning. One way to remove nodes, i.e., potential conduction blocks, from tissue is to change parameters in such a way that the spatial wavelength increases, essentially expelling nodes from the non-pacing site end of the cable. However, unidirectional pinning makes this strategy ineffectual. Thus, we hypothesize that the presence of unidirectional pinning makes spatially discordant alternans more arrhythmogenic than previously thought.
8.2 Possible Laboratory Experiments

In Chapter 6 we presented several numerical experiments that confirmed that the dynamics of the reduced model given by Equations (3.22) and (3.23) are not just artifacts of the reduction, but actual phenomena observable in detailed ionic models. These numerical experiments also suggest possible laboratory experiments. In particular, we confirmed that unidirectional pinning can be observed in the Shifox model. We showed first that this could be done by changing the parameter $\tau$ that scales the timescale of sodium $j$-gate dynamics. However, we also showed that it can be done simply by changing the BCL, a much easier parameter to manipulate in laboratory experiments. Thus, we suggest that a similar experiment be carried out to confirm unidirectional pinning in actual tissue.

As we mention above, an important quantity relating to alternans is the spatial wavelength, which is given by twice the distance between nodes. We also showed in numerical experiments that this wavelength scales sub-linearly with $\Lambda$ in the smooth regime and linearly with $\Lambda$ in the discontinuous regime. Thus, we suggest that experiments in real tissue be carried out to test this hypothesis as well. Since the notion of memory would not be important in these experiments, CV restitution, i.e., an effective $\Lambda$, could be altered at each simulation using drugs to obtain wavelengths for several different simulations, provided that an effective $\Lambda$ value could be computed from the cable’s CV restitution curve.

Finally, we have also studied the values of jumping points at discontinuities in ionic model simulations. We have seen that, in particular, increasing $r$ or $\Lambda$ causes the asymmetry about each node to decrease. A simple experiment could be designed to test this hypothesis in real tissue by simply decreasing the BCL, effectively increasing $r$, once a steady-state discontinuous solution has formed.
8.3 Future Work

We conclude this Thesis with a discussion of potential future work. In our survey of the reduced system given by Equations (3.22) and (3.23) we found two bifurcations. First, we found $r_1(\Lambda)$, describing the onset of alternans. Second, we found $r_2(\Lambda)$, describing the transition from smooth to discontinuous patterns. In Chapter 4 we were able to find an accurate analytical prediction of the onset of alternans $r_1(\Lambda)$ using a linear stability analysis and perturbative techniques. However, such an analytical prediction of the second bifurcation $r_2(\Lambda)$ remains elusive. Thus far, we have only been able to study this bifurcation using numerical techniques presented in Chapter 5. Perhaps a more solid understanding and prediction of this bifurcation can be developed by studying a simplified version of the reduced model given by Equations (3.22) and (3.23). For instance, by setting the APD restitution parameter $\beta$ to zero, we can eliminate $a_n(x)$ yielding the single equation

$$c_{n+1}(x) = -rc_n(x) + c_n^3(x) - \eta \tilde{c}_n(x) + \frac{\eta}{\Lambda} \int_0^x e^{(x'-x)/\Lambda} \tilde{c}_n(x')dx',$$

where $\tilde{c}_n(x) = \int_0^L G(y-x)c_n(y)dy$. This simplified equation still captures the dynamics of the full reduced system. We speculate that perhaps more simplifications can be made to Equation (8.1) such that the dynamics are still captured but $r_2(\Lambda)$ becomes analytically treatable.

Next, in this Thesis we have treated the case of positive calcium-to-voltage coupling. In the reduced model this corresponds to positive values of $\gamma$ in Equation (3.23). Another important case to understand is when this coupling is negative. This would correspond to choosing $\gamma$ to be negative. It remains unclear how this would alter the dynamics of the reduced model. Recall that voltage-to-calcium coupling is always positive, corresponding to a positive value of $\alpha$, so that in this case the parameter $\eta = \alpha \gamma$ becomes negative. We note that physiological hypotheses predict that this would cause a delayed onset of alternans, essentially resulting from the positive and negative voltage-to-calcium and calcium-to-voltage couplings inhibiting each others’ ability to cause alternans [61].

Another related direction of future research is to explore the combined dynamics that result
when the voltage and calcium dynamics, on their own, produce alternans. In terms of our reduced model, this could be modeled with the inclusion of a nonlinear term $a_n^3(x')$ in Equation (3.23) and allowing the APD restitution parameter $\beta$ to take on values greater than one. In this case $\beta$ could be more appropriately thought of as the degree of voltage instability. We note that physiological hypotheses suggest that the resulting dynamics would depend on whether the degree of calcium instability $r$ or the degree of voltage instability $\beta$ is greater [61].

Finally, perhaps the most important extension of this research would be a derivation of a reduced model for alternans not for a one-dimensional cable, but rather a two-dimensional patch of tissue. We note that barring any heterogeneity in tissue or strange geometry effects, cardiac activity typically propagates radially from the pacing site, motivating the one-dimensional case treated in this Thesis. However, real cardiac tissue is heterogeneous and has non-trivial geometries, making the two-dimensional case an important next step. In particular, this would require a realistic modeling of heterogeneities in the tissue, as well as a way to determine the normal vector $\vec{n}$ describing the direction of propagation in the tissue.
Bibliography


Appendix A

Details of the Shifox Ionic Model

In this Appendix we present the detailed formulation of the Shifox model referred to in the Thesis, which was first presented in References [20, 54]. This model combines the calcium-cycling dynamics of Shiferaw et al. [54] with the ionic model of Fox et al. [20]. In the following two sections we will present the details of Fox et al. and the details of Shiferaw et al., respectively. In the third section we will describe the effect of particular parameter choices we have made for use in this Thesis. In particular we will describe how to ensure that alternans are calcium-driven, how to ensure that calcium-to-voltage coupling is positive, and how to change the CV restitution relationship.

A.1 Ionic model of Fox et al.

As described in Chapter 2, we begin with the standard cable equation

\[ \frac{\partial V}{\partial t} = D_V \frac{\partial^2 V}{\partial x^2} - \frac{I_{ion} + I_{stim}}{C_m}, \]  

(A.1)

where \( V(x, t) \) give the transmembrane voltage potential at position \( x \) along the cable at time \( t \). Typically \( x \) and \( t \) are taken to be in units of centimeters and milliseconds, respectively. The constants \( D_V \) and \( C_m \) are the diffusion coefficient and cell capacitance, taken to be \( 5.0 \times 10^{-4} \) cm\(^2\)/ms and \( 1.66 \times 10^{-4} \) \( \mu \)F, respectively. The first term on the right-hand-side of Equation (A.1) \( \frac{\partial^2 V}{\partial x^2} \) describes the diffusion of voltage along the cable, while \( I_{stim} \) accounts for any external stimulus to the cable. We assume that the cable is paced at location \( x = 0 \) with a pacing period BCL.
The ion channel activity then is accounted by the term $I_{ion}$, which is given by the sum of eight separate ion currents

$$I_{ion} = I_{Na} + I_{to} + I_{Kr} + I_{Ks} + I_{Kp} + I_{K1} + I_{Ca} + I_{NaCa}. \quad (A.2)$$

$I_{Na}$ describes the fast sodium current, which is primarily responsible for the sharp spiking behavior that begins each action potential (see Figure 1.2). $I_{to}$, $I_{Kr}$, $I_{Ks}$, $I_{Kp}$, and $I_{K1}$ all represent different potassium ion channels that work in different ways and contribute to different portions of the action potential. $I_{Ca}$ is known as the L-type calcium current and accounts for all the calcium entering the cell from outside. Finally, $I_{NaCa}$ is the sodium-calcium exchanger current, which pumps sodium into the cell at the expense of pumping calcium out of the cell. Below we summarize each current individually.

We begin with the fast sodium current. The total current is given by

$$I_{Na} = g_{Na} m^3 h j (V - E_{Na}), \quad (A.3)$$

where

$$E_{Na} = \frac{RT}{F} \log \left[ \frac{[Na^+]_o}{[Na^+]_i} \right] \quad (A.4)$$

with universal gas constant $R = 8.315 \text{ J/molK}$, temperature $T = 305 \text{ K}$, Faraday constant $F = 96.5 \text{ C/mmol}$, and we have assumed that the internal and external sodium concentrations $[Na^+]_i$ and $[Na^+]_o$ remain constant at 10 and 140 mM, respectively. The fast sodium conductance $g_{Na}$ is assumed to be 12 mS/µF. Finally, $m$, $h$, and $j$ are dynamical gating variables that satisfy ODEs of the form

$$\dot{m} = \frac{m^\infty - m}{\tau_m}, \quad (A.5)$$

$$\dot{h} = \frac{h^\infty - h}{\tau_h}, \quad (A.6)$$

$$\dot{j} = \frac{j^\infty - j}{\tau_j}, \quad (A.7)$$
where \( m^\infty = \alpha_m \) and \( \tau_m = \alpha_m + \beta_m \), and similarly for the \( h \) and \( j \) gates. Each \( \alpha \) and \( \beta \) depends on the voltage \( V \) as follows:

\[
\alpha_m = 0.32 \frac{V + 47.13}{1 - e^{-(V+47.13)/10}},
\]

\[\beta_m = 0.08 e^{-V/11},\]  

\[\alpha_h = 0.135 e^{-(V+80)/6.8},\]  

\[\beta_h = \frac{7.5}{1 + e^{-(V+11)/10}},\]  

\[\alpha_j = \frac{0.175 e^{-(V+100)/23}}{1 + e^{0.15(V+79)}},\]  

\[\beta_j = \frac{0.3}{1 + e^{-(V+32)/10}}.\]  

We note here that since cardiac tissue is an excitable medium, by altering the dynamics of the responsible for the spike at each action potential, we can influence the speed with which stimuli propagate through the cable, i.e., the conduction velocity. To this end, we introduce the parameter \( \tau \) that will scale the timescale \( \tau_j \) (i.e., both \( \alpha_j \) and \( \beta_j \)), which we will change throughout the Thesis. In the final section of this Appendix we provide more details regarding \( \tau \).

We now move onto the equations defining the dynamics of the potassium currents. Beginning with the transient outward potassium current \( I_{to} \), we have

\[I_{to} = g_{to} X_{to} Y_{to} (V - E_K),\]  

where \( g_{to} = 0.1 \text{ mS/}\mu\text{F} \) is the \( I_{to} \) conductance, we assume that the internal and external potassium concentrations \([K^+]_i\) and \([K^+]_o\) remain constant at 149.4 mM and 4.0 mM, respectively, and

\[E_K = \frac{RT}{F} \log \frac{[K^+]_o}{[K^+]_i}.\]  

Similar to \( m, h, \) and \( j \) in the fast sodium current, \( X_{to} \) and \( Y_{to} \) are dynamic gating variables that satisfy

\[\dot{X}_{to} = \frac{X_{to}^\infty - X_{to}}{\tau_{X_{to}}},\]

\[\dot{Y}_{to} = \frac{Y_{to}^\infty - Y_{to}}{\tau_{Y_{to}}},\]  

\[\dot{Z}_{to} = \frac{Z_{to}^\infty - Z_{to}}{\tau_{Z_{to}}}.\]
given by $X^\infty_{to} = \alpha_{Xto}$ and $\tau_{Xto} = \alpha_{Xto} + \beta_{Yto}$ and similarly for the $Y_{to}$ dynamics. The voltage-dependent $\alpha$ and $\beta$ values are given by

$$\alpha_{Xto} = 0.04516e^{0.03577V}, \quad (A.18)$$
$$\beta_{Xto} = 0.0989e^{-0.063237V}, \quad (A.19)$$
$$\alpha_{Yto} = \frac{0.005415e^{-(V+33.5)/5}}{1 + 0.051335e^{-(V+33)/5}}, \quad (A.20)$$
$$\beta_{Yto} = \frac{0.005415e^{-(V+33.5)/5}}{1 + 0.051335e^{-(V+33)/5}}. \quad (A.21)$$

The inward rectifier current $I_{K1}$ is given by the simpler formulation

$$I_{K1} = g_{K1}K^\infty_1 \frac{[K^+]_o}{[K^+]_o + 13} (V - E_K), \quad (A.22)$$

where

$$K^\infty_1 = \frac{1}{2 + e^{1.62F/(RT)(V-E_K)}}, \quad (A.23)$$

and $g_{K1} = 42 \text{ mS/\mu F}$ is the inward rectifier current conductance.

The delayed rectifier current is then broken up into a rapid and slow component. The rapid component $I_{Kr}$ is given by

$$I_{Kr} = g_{Kr}\sqrt{\frac{[K^+]_o}{2}} x_{Kr} \frac{V - E_K}{1 + 2.5e^{(V+28)/10}}, \quad (A.24)$$

where $g_{Kr} = 0.0136 \text{ mS/\mu F}$ is the rapid delayed rectifier conductance. The dynamic gating variable $x_{Kr}$ satisfies

$$\dot{x}_{Kr} = \frac{x^\infty_{Kr} - x_{Kr}}{\tau_{Kr}}, \quad (A.25)$$

where

$$x^\infty_{Kr} = \frac{1}{1 + e^{-2.182-0.1819V}}, \quad (A.26)$$
$$\tau_{Kr} = 43 + \frac{1}{e^{-5.495+0.1601V} + e^{-7.677-0.0128V}}. \quad (A.27)$$

The slow component of the delayed rectifier current $I_{Ks}$ is given by

$$I_{Ks} = g_{Ks}x^2_{Ks}(V - E_{Ks}), \quad (A.28)$$
where \( g_{Ks} = 0.0245 \text{ mS/\mu F} \) is the slow delayed rectifier conductance and

\[
E_{Ks} = \frac{RT}{F} \log \frac{[K^+]_o + 0.01833[Na^+]_o}{[K^+]_i + 0.01833[Na^+]_i}.
\] (A.29)

The dynamic gating variable \( x_{Ks} \) satisfies

\[
\dot{x}_{Ks} = \frac{x_{Ks}^\infty - x_{Ks}}{\tau_{Ks}},
\] (A.30)

where

\[
x_{Ks}^\infty = \frac{1}{1 + e^{-(V-16)/13.6}},
\] (A.31)

\[
\tau_{Ks} = \frac{1}{\frac{0.0000719(V-10)}{1-e^{-0.748(V-10)}} + \frac{0.00031(V-10)}{1+e^{0.0687(V-10)}}}.
\] (A.32)

The formulation of the plateau potassium current \( I_{Kp} \) is relatively simple and given by

\[
I_{Kp} = g_{Kp} \frac{V - E_K}{1 + e^{(7.488-V)/5.98}},
\] (A.33)

where \( g_{Kp} = 0.00221 \text{ mS/\mu F} \) is the plateau potassium conductance.

Finally, the formulation for both the L-type calcium current \( I_{Ca} \) and the sodium-calcium exchanger current \( I_{NaCa} \) are defined in terms of their respective ion fluxes \( J_{Ca} \) and \( J_{NaCa} \) via the conversions

\[
I_{Ca} = -2 F v_i J_{Ca} / C_m,
\] (A.34)

\[
I_{NaCa} = F v_i J_{NaCa} / C_m,
\] (A.35)

where \( v_i = 2.58 \times 10^{-5} \text{ \mu l} \) is the cell volume. Furthermore, we need to introduce the variable \( c_s \) that gives the calcium concentration in the submembrane space, i.e., the part of the cell near the cell membrane. The break up of intracellular compartments will be explained in detail in the next section when we describe the calcium-cycling currents.

The L-type calcium flux, which is the primary mechanism for calcium entering the cell from outside, is given by

\[
J_{Ca} = -g_{Ca} df_{Ca} f 4VF^2 c_s e^{2a} - 0.341[Ca^{2+}]_o e^{2a} - 1,
\] (A.36)
where \( g_{Ca} = 1.46^{-3} \mu \text{Ml/C/ms} \) is the strength, \([Ca^{2+}]_o = 1.8 \text{ mM} \) is the external concentration of calcium, and \( a = VF/RT \). The dynamic gating variables \( d, f_{Ca} \), and \( f \) satisfy

\[
\dot{d} = \frac{d^\infty - d}{\tau_d},
\]

\[
\dot{f}_{Ca} = \frac{f_{Ca}^\infty - f_{Ca}}{\tau_{fCa}},
\]

\[
\dot{f} = \frac{f^\infty - f}{\tau_f},
\]

where \( \tau_d = 5 \text{ ms} \), \( \tau_{fCa} = 20 \text{ ms} \), and \( \tau_f = 30 \text{ ms} \), and

\[
d^\infty = \frac{1}{1 + e^{-(V+5)/6.24}},
\]

\[
f_{Ca}^\infty = \frac{1}{1 + \gamma},
\]

\[
f^\infty = \frac{1}{1 + e^{(V+35)/8.6}},
\]

where \( \gamma = 0.2 \). We note briefly that the voltage-dependent inactivation timescale \( \tau_f \) and the calcium inactivation exponent \( \gamma \) are chosen so that alternans are calcium-driven, which we explain in greater detail below.

Finally, the sodium-calcium exchanger flux \( J_{NaCa} \), which pumps sodium into the cell while it pumps calcium out of the cell, is given by

\[
J_{NaCa} = \frac{1}{K_{m,Na}^3 + [Na^{+}]_o^3} \frac{1}{K_{m,Ca} + [Ca^{2+}]_o} \frac{e^{0.35a[Na^{+}]_o^2[Ca^{2+}]_o} - e^{-0.65a[Na^{+}]_o^2c_s}}{1 + e^{-0.65a/10}},
\]

where \( K_{m,Na} = 87.5 \text{ mM} \) and \( K_{m,Ca} = 1.38 \text{ mM} \).

### A.2 Calcium-cycling dynamics of Shiferaw et al.

The main feature of the Shifox model that allows for us to ensure calcium-driven alternans is the calcium-cycling dynamics of Shiferaw et al. [54]. Importantly, the cell is broken up into several different compartments and we measure the concentration of calcium in each. In addition to the calcium concentration outside the cell \([Ca^{2+}]_o \), which we assume is constant at 1.8 mM, we consider four distinct compartments. These compartments are illustrated in Figure A.1. The myoplasm,
i.e., the interior of the cell that does not include the sarcoplasmic reticulum (SR), is broken up into the sub-membrane space and the bulk myoplasm, or interior, space. The concentrations in the sub-membrane and interior space are, respectively, $c_s$ and $c_i$. This division is important due to the fact that calcium entering the cell both from outside and from the SR enters the sub-membrane space, i.e., the space near the cell membrane. Once in the sub-membrane space, calcium can then diffuse into the interior space.

The function of the SR is to store calcium, and upon the influx of calcium via the L-type calcium current, release the stored calcium into the cell myoplasm. The SR consists of rigid tube-like structures that extend throughout the cell. When the SR releases calcium, it does so in response to sensing calcium entering the sub-membrane space via L-type calcium current with bulb-like junctions that are located near the cell membrane. In total, these junctions comprise the junctional SR (JSR). The remainder of the SR comprises the bulk SR (NSR). In Figure A.1 we illustrate all the separate compartments that store calcium. To measure the calcium concentration in each SR compartment, we use $c'_j$ to describe the average concentration in each JSR and $c_j$ to describe the concentration of calcium in the entire SR (JSR plus NSR). Finally, the release flux of calcium from the SR to the myoplasm, i.e., from the JSR to the Sub-membrane space is described the quantity $J_{rel}$, which evolves according to its own ODE.

![Figure A.1: Illustration of the cellular compartments involved in the calcium cycling model of Shiferaw et al. [54].](image-url)
Beginning in the sub-membrane space, $c_s$ evolves according to

$$
\dot{c}_s = \beta_s \frac{v_i}{v_s} \left( J_{rel} - \frac{c_s - c_i}{\tau_s} + J_{Ca} + J_{NaCa} \right),
$$

(A.44)

where $v_i/v_s = 10$ is the ratio of bulk volume to sub-membrane volume, and $\beta_s$ describes the buffering of calcium to the SR, Calmodulin, and Troponin, and is given by

$$
\beta_s = \left[ 1 + \frac{B_{SR}K_{SR}}{(c_s + K_{SR})^2} + \frac{B_{Cd}K_{Cd}}{(c_s + K_{Cd})^2} + \frac{B_TK_T}{(c_s + K_T)^2} \right]^{-1},
$$

(A.45)

where $B_{SR} = 47 \mu\text{mol/l}$, $B_{Cd} = 24 \mu\text{mol/l}$, and $B_T = 70 \mu\text{mol/l}$ give the total concentration of SR binding sites, Calmodulin binding sites, and Troponin, and $K_{SR} = 0.6 \mu\text{M}$, $K_{Cd} = 7 \mu\text{M}$, and $K_T = 0.6 \mu\text{M}$ give the dissociation constants for SR binding sites, Calmodulin binding sites, and Troponin. The four terms on the right hand-side of Equation (A.44) describe the calcium that enters from the JSR, the calcium that diffuses between the sub-membrane and bulk space, the calcium that enters via the L-type calcium current, and the calcium that enters via the sodium-calcium exchanger. The parameter $\tau_s = 2 \text{ ms}$ gives the timescale of diffusion between the sub-membrane and bulk spaces.

Next, in the bulk space we have that $c_i$ evolves according to

$$
\dot{c}_i = \beta_i \left( \frac{c_s - c_i}{\tau_s} - J_{up} \right),
$$

(A.46)

where $\beta_i$ is a similar buffering term as $\beta_s$, and is given by

$$
\beta_i = \left[ 1 + \frac{B_{SR}K_{SR}}{(c_i + K_{SR})^2} + \frac{B_{Cd}K_{Cd}}{(c_i + K_{Cd})^2} + \frac{B_TK_T}{(c_i + K_T)^2} \right]^{-1}.
$$

(A.47)

The two terms on the right hand-side of Equation (A.46) describe the diffusion of calcium between the sub-membrane and bulk space and a small uptake flux $J_{up}$ describing the uptake of calcium from the bulk space into the JSR. $J_{up}$ is given by

$$
J_{up} = \frac{v_{up}c_i^2}{c_i^2 + c_{up}^2},
$$

(A.48)

where $v_{up} = 0.25 \mu\text{M/ms}$ is the strength of the uptake flux and $c_{up} = 0.5 \mu\text{M}$ is the uptake threshold.
Next, in the SR we have that \( c_j \) depends on the release flux \( J_{rel} \) and the uptake flux \( J_{up} \)

\[
\dot{c}_j = -J_{rel} + J_{up}.
\]

Furthermore, the calcium concentration in the JSR \( c'_j \) equilibrates with the rest of the SR according to

\[
\dot{c}'_j = \frac{c_j - c'_j}{\tau_a},
\]

where \( \tau_a = 50 \text{ ms} \) is the timescale of this relaxation.

Finally, the release flux \( J_{rel} \) of calcium from the JSR into the sub-membrane space evolves according to

\[
\dot{J}_{rel} = gJ_{Ca}Q(c'_j) - J_{rel}/\tau_s,
\]

where \( \tau_s = 20 \text{ ms} \) and \( g = 7.5 \times 10^5 \text{ sparks/\mu M} \) is the flux strength. In particular, the release flux is triggered by the L-type calcium flux \( J_{Ca} \), which is multiplied by the function \( Q(c'_j) \). The function \( Q(c'_j) \) is given by the piecewise formulation

\[
Q(c'_j) = \begin{cases} 
0 & \text{if } 0 \leq c'_j < 50 \\
\frac{3}{2}(c'_j - 50) & \text{if } 50 \leq c'_j < 110 \\
u c'_j + s & \text{if } c'_j \geq 110,
\end{cases}
\]

where \( s = 90 - 110u \) is chosen to make \( Q(c'_j) \) continuous. Thus, the parameter \( u \) gives the slope of SR release if \( c'_j \geq 110 \), which, for larger \( u \) amplifies the instability in the calcium dynamics. In this Thesis we choose a relatively large value of \( u = 9 \text{ ms}^{-1} \), which we will describe below.

### A.3 Parameter Choices for Calcium-Driven Alternans

The advantage of using the Shifox model is that the formulations of Shiferaw et al. and Fox et al. allow us to choose parameter values to ensure that alternans are calcium-driven. To this end, there are two important parameters: the rate of calcium release from the SR into the myoplasm, and the voltage-inactivation timescale. The rate of calcium increase can be manipulated by changing
the parameter $u$, which describes the slope of $Q$ at large values of $c_j'$ [see Equations (A.51) and (A.52)]. In particular, a larger slope $u$ corresponds to a larger degree of instability in the calcium-cycling dynamics. Thus, we choose a relatively large value $u = 9 \text{ ms}^{-1}$ to ensure a large calcium instability. Furthermore, the timescale $\tau_f$, which appears in the L-type calcium current [specifically in Equation (A.39)] describes the timescale of voltage-inactivation, i.e., the time needed for the voltage dynamics to “rest” between beats. Thus, we choose a relatively small value of $\tau_f = 30 \text{ ms}$ to ensure a small degree of instability in the voltage dynamics. Thus, by choosing relatively large and small $u$ and $\tau$ parameter values, we effectively amplify and suppress instabilities in the calcium and voltage dynamics, respectively, ensuring that when alternans are observed, they are calcium-driven.

In addition to ensuring that alternans are calcium-driven, we also wish to ensure that the calcium-to-voltage coupling is positive. Voltage and calcium dynamics primarily interact through the L-type calcium current, and therefore the nature of this coupling can be manipulated by changing the exponent $\gamma$ in Equation (A.41). In particular, choosing $\gamma < 1$ typically yields a positive coupling, while choosing $\gamma > 1$ typically yields a negative coupling [31, 51]. Thus, in our simulations we choose $\gamma = 0.2$.

Finally, we also wish to have a mechanism to change the CV restitution function. Since a cable of cardiac tissue is an excitable medium, the conduction velocity depends strongly on the spiking behavior at the beginning of each action potential (see Figure 1.2). Since the fast sodium current $I_{Na}$ is primarily responsible for this part of the action potential, by changing the timescales of these dynamics we can change CV restitution. In particular, by scaling the timescale $\tau_j = \alpha_j + \beta_j$ [Equations (A.12) and (A.13)] up by a scaling constant $\tau$ the CV restitution curve become less flat throughout [31, 51, 52], as we see in Figure 2.11.
Appendix B

Analysis of Smooth Alternans Profiles: Asymmetric Greens Function

This appendix is a brief extension of the analysis of Chapter 4, generalizing the onset of alternans and spatial properties of smooth solutions to the case of non-zero asymmetry \( w \) in the Green’s function. Thus, we consider the case of a non-zero \( w \) in the Green’s function given in Equation (3.6). For simplicity, we will assume that the APD restitution parameter \( \beta \) is zero. Our goal is to describe the onset of alternans \( r_1(\Lambda) \), as well as the spatial properties of smooth wave patterns after onset, in particular the spatial wavelength \( \lambda_s \) and velocity \( v \).

As in Chapter 4, we begin by assuming perturbations of the form \( c_n(x) = c\lambda^ne^{ikx} \) and \( a_n(x) = a\lambda^ne^{ikx} \). The result from inserting these into Equation (3.22) remains the same, yielding Equation (4.1). However, since the degree of asymmetry \( w \) is no longer zero, the Green’s function is no longer a Gaussian, inserting these perturbations into Equation (3.23) yields

\[
a = \gamma ce^{-k^2\xi^2/2} \left[ 1 + \frac{ikw}{4}(1 - k^2\xi^2) \right].
\]  

Combining Equations (4.1) and (B.1), we eliminate \( c \) and \( a \) and find that in terms of the wave number \( k \), the growth parameter \( \lambda \) is given by

\[
\lambda = -r + \eta \left( \frac{\epsilon}{ik + \epsilon} - 1 \right) e^{-k^2\xi^2/2} \left[ 1 + \frac{ikw}{4}(1 - k^2\xi^2) \right].
\]  

Because we are considering a cable of finite length, we still impose the condition of an absolute instability, which is given by \( \frac{\partial \lambda}{\partial k} = 0 \). Thus, setting the derivative of Equation (B.2) equal to zero yields the relatively complicated equation

\[
4i\epsilon - ik^2(w - 4\epsilon\xi^2) - 2kw\epsilon + k^3(3w\epsilon - 4) + 2ik^4w\xi^2 + k^5w\epsilon^2 + ik^6w\xi^4 = 0.
\]  

(B.3)
To leading order, this equation is balanced by a purely real wave number \( k = 2\sqrt{\epsilon/w} \). Finally, we expand Equation (B.2), and find that, to first order,

\[
\lambda = -r - \eta + \eta \frac{\xi^2}{w\Lambda},
\]

(B.4)

where \( \xi^2/(w\Lambda) \) is a dimensionless parameter that relates the ratio of the square of the length scale of electrotonic coupling to the product of the length scales of CV restitution and asymmetry of the Green’s function. Setting \(|\lambda| = 1\), we find that the onset of alternans is given by

\[
 r = r_1(\Lambda) \equiv 1 - \eta + \eta \frac{\xi^2}{w\Lambda},
\]

(B.5)

We now consider the spatial properties of solutions near the onset of alternans. Recall first that since \( c_n(x) \propto \lambda^n e^{ikx} = e^{-k_{im}x} e^{i\Omega(x+n\Omega/k_{Re})} \), where \( \lambda = -e^{i\Omega} \), then the spatial wavelength is given by \( \lambda_s = 2\pi/k_{Re} \) and the velocity is given by \( v = \Omega/k_{Re} \approx \lambda_{Im}/k_{Re} \). However, both the growth parameter \( \lambda \) and the wave number \( k \) are purely real to first-order. Thus, the velocity \( v \) of solutions near onset is zero, i.e., solutions are stationary, and the spatial wavelength \( \lambda_s \) is given by

\[
\lambda_s = \pi\sqrt{w\Lambda}.
\]

(B.6)

In addition to characterizing the onset of alternans \( r_1(\Lambda) \), spatial wavelength \( \lambda_s \), and velocity \( v \) of solutions near onset for the case of finite \( w \), these results serve as a connection between voltage-driven alternans and calcium-driven alternans. We saw in Chapter 4 that up to scaling and translation by the cross-coupling parameter \( \eta \), the onset of alternans \( r_1(\Lambda) \), as well as spatial wavelength \( \lambda \) and velocity \( v \) of alternans near onset agreed. In fact, in Reference [16], Echebarria and Karma found that the onset of alternans for a finite asymmetry parameter \( w \) differs from that for \( w = 0 \). Furthermore, they found that in this case, the resulting profiles formed smooth stationary waves (i.e., zero velocity) and that the onset value \( r_1(\Lambda) \) and spatial wavelength \( \lambda_s \) match those in Equations (B.5) and (B.6). Thus, we have further evidence that calcium-driven alternans realized at relatively mild degrees of calcium instabilities are analogous to voltage-driven alternans that have been previously studied.
Appendix C

ODE Approach to Spatial Scaling of Discontinuous Solutions

This appendix serves as a brief outline of the ODE approach for describing the spatial scaling of solutions in the discontinuous regime. Our goal is to find and solve a differential equation that predicts the shape and scaling of solutions. Recall from Chapter 5 that Equation (5.4) was found after assuming stationary period-two solutions of the form $-c_{n+1}(x) = c_n(x) = c(x)$ and $-a_{n+1}(x) = a_n(x) = a(x)$. Assuming as well a zero APD restitution parameter $\beta$ and a zero asymmetry value $w$, Equations (3.22) and (3.23) yield

\[
[(r - 1) - 3c^2(x)]c'(x) + \alpha a'(x) = \frac{1}{\Lambda}[c^3(x) - (r - 1)c(x)], \tag{C.1}
\]

\[
a(x) = \frac{\gamma}{\sqrt{2\pi \xi}} \int e^{-\frac{(x' - x)^2}{2\xi^2}} c(x')dx'. \tag{C.2}
\]

In order to find a single differential equation for $c(x)$, we seek to use Equation (C.2) to approximate $a(x)$ in terms of $c(x)$ so that we may eliminate $a'(x)$ from Equation (C.1). We begin by making the change of variables $z = (x' - x)/\xi$, which yields

\[
a(x) = \frac{\gamma}{\sqrt{2\pi}} \int e^{-\frac{z^2}{2}} c(x + \xi z)dz. \tag{C.3}
\]
Next, we Taylor-expand $c(x + \xi z)$ about $z = 0$, obtaining the series form

$$a(x) = \frac{\gamma}{\sqrt{2\pi}} \int e^{-z^2/2} \left[ \sum_{k=0}^{\infty} \frac{\xi^k c^{(k)}(x)}{k!} z^k \right] dz$$

(C.4)

$$= \frac{\gamma}{\sqrt{2\pi}} \int e^{-z^2/2} \left[ \sum_{k=0}^{\infty} \frac{\xi^{2k} c^{(2k)}(x)}{(2k)!} z^{2k} \right] dz$$

(C.5)

$$= \gamma \sum_{k=0}^{\infty} \frac{\xi^{2k} c^{(2k)}(x)}{(2k)!} \int e^{-z^2/2} \sqrt{\frac{2\pi}{2\pi}} z^{2k} dz$$

(C.6)

$$= \gamma \sum_{k=0}^{\infty} \frac{\xi^{2k} c^{(2k)}(x)}{(2k)!} E[z^{2k}],$$

(C.7)

where $c^{(k)}(x)$ denotes the $k^{th}$ derivative of $c(x)$ with respect to $x$, $E[z^k]$ is the $k^{th}$ moment of $e^{-z^2/2}/\sqrt{2\pi}$, and all odd moments of $e^{-z^2/2}/\sqrt{2\pi}$ vanish. We note first that to eliminate the $a'(x)$ term in Equation (C.1), we must take a derivative of Equation (C.7). Also, each additional term in the summation involves a higher-order derivative of $c(x)$. Thus, there is a trade-off between the accuracy of the approximation, i.e., how many terms of the summation to keep, and avoiding high order derivative terms in the final equation.

First, we consider the zeroth-order approximation, i.e., using only the first term in Equation (C.7). This approximation is equivalent to assuming that on the scale of $\Lambda$, the Green’s function acts as a delta function, i.e., $G(x, x') = e^{-(x' - x)^2/2\xi^2}/\sqrt{2\pi \xi^2} \approx \delta(x' - x)$, and yields $a(x) \approx \gamma c(x)$. Since $\xi \ll \Lambda$, this approximation is accurate where $c(x)$ is slowly varying, i.e., away from the nodes. The resulting ODE is then

$$[(r - 1) - 3c^2(x) + \eta]c'(x) = \frac{1}{\Lambda}[c^3(x) - (r - 1)c(x)].$$

(C.8)

We next reduce the parameters in Equation (C.8) by multiplying through by $\xi$, rescaling space by $y = x/\Lambda$, and defining $\tilde{c}(y) = c(\Lambda y)$. For notational convenience, we drop each $\sim$ and replace $y$ with $x$. A non-dimensional small parameter $\epsilon = \xi/\Lambda$, characterizing the ratio of the length scale of electrotonic coupling to the lengthscales of CV restitution, appears on each side of the equation. After canceling each $\epsilon$, we arrive at

$$[(r - 1) - 3c^2(x) + \eta]c'(x) = [c^3(x) - (r - 1)c(x)].$$

(C.9)
Equation (C.9) is nonlinear but separable, allowing us to solve for $c(x)$ implicitly. Assuming an initial condition of $c(0) = c_0$ we find

$$x = \frac{1}{2(r-1)} \left[ (\eta - 2(r-1)) \log \left( \frac{c^2(x) - (r-1)}{c_0^2 - (r-1)} \right) - 2(r-1 + \eta) \log \left( \frac{c(x)}{c_0} \right) \right].$$  \hfill (C.10)

Finally, the initial condition $c(0)$ can be found by noting that at $x = 0$ the integral term in Equation (3.22) vanishes, so that for a stationary solution with $a(x) = \gamma c(x)$ we have that $c(0) = \pm \sqrt{r-1 + \eta}$, giving

$$x = \frac{1}{2(r-1)} \left[ (\eta - 2(r-1)) \log \left( \frac{c^2(x) - (r-1)}{\eta} \right) - 2(r-1 + \eta) \log \left( \frac{c(x)}{\sqrt{r-1 + \eta}} \right) \right].$$  \hfill (C.11)

We now compare the solution of the zeroth-order ODE, given by Equation (C.11) to simulations of Equations (3.22) and (3.23). In Figure C.1 we plot the solution to the zeroth-order ODE in dashed red and the results from simulation in blue. Parameters are $r = 1.2$, $\Lambda = 30$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$. The solution of the zeroth-order ODE captures well the shape of the profile initially, away from the node. However, as the profile nears the node and begins to decrease in slope more abruptly, the solution of the zeroth-order ODE begins to fail.

![Figure C.1: Results from the zeroth-order ODE approach: The solution given by Equation (C.11) (dashed red) vs simulation of Equations (3.22) and (3.23). Parameters are $r = 1.2$, $\Lambda = 30$, $\alpha, \gamma = \sqrt{0.3}$, $\beta = 0$, $\xi = 1$, and $w = 0$.](image)

To improve upon the shortcomings of the zeroth-order ODE approach, we now consider including the second-order term in the summation of Equation (C.7). This yields the approximation
\( a(x) \approx \gamma c'(x) + \gamma \xi^2 c''(x)/2 \), which after taking a derivative and inserting into Equation (C.1), yields an ODE that is nonlinear and third-order. We next reduce parameters in the same manner as above, after which we obtain the following ODE

\[
(r-1) - 3c^2(x) + \eta c'(x) + \frac{\eta^2}{2} c''(x) = [c^3(x) - (r-1)c(x)].
\] (C.12)

Because Equation (C.12) is third order, we need initial conditions \( c(0), c'(0), \) and \( c''(0) \). Furthermore, because the zeroth-order approximation \( a(x) = \gamma c(x) \) accurately captured the shape of \( c(x) \) near the origin [see Figure C.2], we again use \( a(x) = \gamma c(x) \) to find the necessary initial condition. In addition to \( c(0) = \sqrt{r-1+\eta} \), we find that \( c'(0) = -\frac{\eta}{2\sqrt{r-1+\eta}} \) and \( c''(0) = \frac{\eta(r-1)}{2(r-1+\eta)^{3/2}} \).

Figure C.2: Results from the second-order ODE approach: Numerical solution of Equation (C.12) (dashed green) compared to the zeroth-order solution given by Equation (C.11) (dashed red) and simulation of Equations (3.22) and (3.23). Parameters are \( r = 1.2, A = 30, \alpha, \gamma = \sqrt{0.3}, \beta = 0, \xi = 1, \) and \( w = 0. \)

Given its nonlinearity and high-order, the second-order ODE given in Equation (C.12) is difficult to solve analytically. Furthermore, it is a singular perturbation of Equation (C.9), for which only an implicitly-defined solution \( c(x) \) exists, making any perturbative solution also very difficult to obtain. Thus, we need to proceed in solving Equation (C.12) numerically. In Figure C.2 we plot the solution to the second-order ODE, computed numerically in dashed green, and compare with the solution to the zeroth-order ODE and simulations, plotted in dashed red and blue, respectively. Like the solution to the zeroth-order ODE, the solution to the second-order ODE matches up very well away from the node. Furthermore, the solution to the second-order ODE approves upon that
to the zero\textsuperscript{th}-order ODE, as it qualitatively agrees with the results from simulation near the node as the slope begins to decrease abruptly.

We close this appendix with a few brief remarks. First, we find that the second-order ODE given by Equation (C.12) is very stiff to solve. Thus, it is very sensitive to small changes in the initial values $c(0)$, $c'(0)$, and $c''(0)$, as well as the numerical method used to solve it. This is most likely due to the fact that the ODE is third order, and in fact a singular perturbation of the zero\textsuperscript{th}-order ODE given by Equation (C.9). Thus, we expect that the resulting fourth-order ODE from including an additional term from Equation (C.7) will yield an even stiffer ODE. Second, we note that after obtaining solutions from both the zero\textsuperscript{th}- and second-order ODEs, we need to rescale $x$ by $\Lambda$ to match up with the results from simulations. Thus, despite not obtaining an analytical description of the scaling of solutions, we confirm that solutions scale linearly with $\Lambda$. 